National Clinical Guideline Centre

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Hepatitis B (chronic)

Appendices E - G

Hepatitis B Guideline

Appendices

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Final

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Royal College of Physicians
Setting higher medical standards
Royal College of Nursing
RCGP Royal College of General Practitioners
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Appendix E: Clinical evidence tables

E.1 Patient Information

Reference	Study type/ Study quality	Number of patients	Population	Group 1 (cases)	Group 2 (controls)	Length of follow-up	Outcome measures	Source of funding
Noghabi AA and Zandi M et al. The effect of education on quality of life in patients under interferon therapy. Hepar Mon 2010; 10(3): 218-222	Quasi-experimental study (pre-test post-test method) Patients were randomly assigned into two groups. Study quality: Indirect population (<40% hep B patients)	N=60	Setting: Hepatitis centre, Iran Method: sampling was non-randomised and based on sample characteristics (see inclusion) Inclusion: age 18-60 years, absence of other infections and chronic diseases, first time treatment for Interferon alpha therapy and absence of cirrhosis Exclusion: -	Education sessions + pamphlets Classes were held once a week and in each class educational pamphlets were distributed among the cases. Each education session (45 minute each) had a maximum of 6 patients and 6 accompanying persons. These accompanying persons had a supportive care role. 1st session The nature of their disease, transmission routes, the diagnosis and treatment of their disease were explained and pamphlets were distributed to the patients. 2nd session The effect of IFN therapy on their disease, the frequent side effects after injection, methods of protecting themselves and controlling these side effects were explained and pamphlets were	After the study, educational pamphlets were distributed to the control group for ethical reasons and the correct method of injection of interferon was also taught to them. (n=30)	12 weeks Education session: one month	Self-reported Quality of life (QoL) at the time of entering the study and 12 weeks after therapy – QoL questionnaire for patients with chronic liver disease (CLDQ) – includes fatigue, activity, emotional symptoms, abdominal symptoms, systemic symptoms and worry. Score are graded from 1 to 7 for each category making the minimum possible scores 29 and the maximum 203 (validated) (the higher score the better) Follow up of patients	Tehran University of Medical Sciences and Baqiyatallah Research center for gastroenterology and liver disease.

				distributed. 3rd session The method of the self-injection of IFN was explained and the patients' questions were answered. 4th session The injection by IFN by the patient was observed and their problems, if any, were corrected. (n=30)			was done as self – reporting with in-person attendance every month	

Baseline characteristics

	Cases (n=30)	Controls (n=30)	P value
Age	40.3 ± 14.9	37.2 ± 9.5	0.33
Sex, M/F n(%)	22 (73.3)/ 8 (26.7)	24 (80)/ 6 (20)	0.381
Level of education Illiterate Primary and guidance school Diploma and higher	 3 (10) 16 (53.3) 11 (36.7)	 0 15 (50) 15 (15)	 0.19
Marital status Single Married	 13 (43.3) 17 (56.6)	 15 (50) 15 (50)	 0.398
Number of children 3 or less >3	 23 (76.7) 7 (23.3)	 28 (93.3) 2 (6.7)	 0.145
Occupation Worker	 4 (13.3)	 7 (23.3)	 0.076

Employee Housekeeper Student Retired	6 (20) 4 (13.3) 6 (20) 10 (33.3)	4 (13.3) 4 (13.3) 0 15 (50)	
Duration of disease 1-3y 3-6y >6y	 21 (70) 5 (16.7) 4 (13.3)	 22 (73.3) 4 (13.3) 4 (13.3)	 1.0
Hospitalisation None Once	 30 (100) 0	 28 (93.3) 2 (6.72)	 0.492
Hepatitis type HBV HCV	 6 (20) 24 (80)	 10 (33.3) 20 (66.7)	 0.243

No significant difference was found between the two groups

Results (before and after 12 weeks follow up)

Quality of life before and after 12 weeks (3 months) within groups

	Cases			Controls		
	Before	After	P (Wilcoxon test)	Before	After	P (Wilcc
Score (min-max)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Abdominal symptoms (3-21)	17.7 (3.1)	19.5 (3.2)	0.00	15.9 (5.3)	15.9 (5.6)	0.48
Activity (3-21)	20 (1.9)	18 (3.6)	<0.001	19.8 (1.9)	18.7 (2.7)	0.01
Fatigue (5-35)	26.3 (6.3)	26 (6.9)	0.08	23.4 (8)	23 (7.2)	0.68
Systemic symptoms (5-35)	29.9 (4.1)	29.1 (5.1)	0.29	28.5 (5.2)	26.4 (6.6)	0.03
Emotional (8-56)	40.1 (9.2)	46.5 (10.6)	<0.001	33.3 (9.9)	33 (9.2)	0.03
Worry (5-35)	24.1 (5.3)	30.2 (6.3)	<0.001	22.3 (6.8)	21.9 (7.4)	0.21
Total (29-203)	158.6 (21.4)	170 (23.6)		154.5 (28.5)	136.9 (30.6)	

Quality of life before and after 12 weeks (3 months) between the two groups

	Before intervention			After intervention		
	Cases	Controls	P (Mann-Whitney test)	Cases	Controls	P (Mann test)
Score (min-max)	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Abdominal symptoms (3-21)	17.7 (3.1)	15.9 (5.3)	0.43	19.5 (3.2)	15.9 (5.6)	0.94
Activity (3-21)	20 (1.9)	19.8 (1.9)	0.8	18 (3.6)	18.7 (2.7)	0.08
Fatigue (5-35)	26.3 (6.3)	23.4 (8)	0.26	26 (6.9)	23 (7.2)	0.84
Systemic symptoms (5-35)	29.9 (4.1)	28.5 (5.2)	0.35	29.1 (5.1)	26.4 (6.6)	0.04
Emotional (8-56)	40.1 (9.2)	33.3 (9.9)	0.006	46.5 (10.6)	33 (9.2)	0.8
Worry (5-35)	24.1 (5.3)	22.3 (6.8)	0.06	30.2 (6.3)	21.9 (7.4)	0.64
Total (29-203)	158.6 (21.4)	154.5 (28.5)		170 (23.6)	136.9 (30.6)	

The quality of life score in the cases showed a significant increase after 12 weeks compared to the controls.

Study limitations: mixed population; different treatment regimens in hepatitis B and C (IFN alpha + Ribavirin in hep C and IFN alpha in hep B) and this has not been taken into account in this study.

Authors' conclusion: This study showed that continuous education and follow up in chronic hepatitis B and C patients under IFN alpha treatment could greatly increase their adherence to IFN treatment and decrease the side effects, ultimately resulting in a better quality of life.

Reference	Study type/ Study quality	Number of patients	Population	Length of follow-up	Outcome measures	Source of funding
Ho A and Tan T. Pregnant women and their willingness to be treated for hepatitis B during pregnancy. AASLD	Cross-sectional survey (abstract)	N=60 75 patients were asked to participate in the study, 60	Setting: an Asian population; USA Methods: a translated questionnaire was given to pregnant women in waiting rooms at various obsterics/ gynecology clinics with a large Asian population	Not applicable	% people that would take hepatitis B medication during pregnancy % people who planned on breastfeeding	Not stated

abstracts. 2011: Su 1003	Study quality: Very low	completed questionnaires.	were targeted because of the high incidence of hepatitis B in that group. The questionnaire obtained information on demographic characteristics, obstetric history, family history of HBV, personal history of HBV, perceptions of treatment and risks, including breastfeeding. Population characteristics Mean age 32 years (range 21-44) 55 (91%) were of Asian ethnicity 93% of patients were born outside of the USA. 57% of patients were born outside of the US had been in the US <10 years. >79% patients had at least a college degree. Average number of pregnancies was 2 Average week of gestation was 29 weeks			

Results
67% (95% CI 55-79%) reported they would take hepatitis B medication while pregnant.
All respondents (100%) planned on breastfeeding, but 58% (95%CI 46-70%) stated that they would not breastfeed if they knew they had hepatitis B.
>97% stated their reason was that they would be afraid to transmit hepatitis B to their baby.

Conclusion: Most women were interested in taking antiviral therapy for hepatitis B while pregnant, likely motivated by a desire to reduce perinatal transmission.

Patients still perceive a high risk of HBV transmission via breastfeeding despite current recommendations further supporting the need for patient education.

E.2 Settings for pre therapeutic tests

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Length of follow-up	Outcome measures	Source of funding
Smith 2010	Retrospective (abstract) Study quality: Inadequate information on recruitment No baseline table No. excluded do not add up	Initial N=2698 Final N=1094 Duplicate requests (including from within hepatology), indeterminate (n=18) Untraceable confidential hospital numbers used by the sexual health clinic (n=459)	Recruitment/setting: St Mary's Hospital, Imperial College Healthcare NHS Trust, London UK Inclusion: Patients found to be HBsAg positive by both primary care and hospital clinicians (HBsAg data obtained by the virological department at St Mary's Hospital over a 3 year period from Jan 2007 to Dec 2009). Source of data: primary care, hospital out-patient, in-patient, Accident and Emergency or ante-natal clinic. Exclusion: Duplicate tests, equivocal serology and unidentifiable patients were excluded. Baseline characteristics – information not given	Not applicable	Proportion (%) of patients attended at least one hepatology clinic (or referred to specialist care)	Not stated

Results

Patients tested in primary care were less likely to be referred to specialist care.

In-hospital referral rates are better.

Request site	n/N (%) did not reach hepatology clinic (specialist care)
Hospital	81/912 (9%)

Primary care	151/182 (83%)

Additional results: Antenatal patients were the commonest group tested in the hospital setting who failed to be referred to specialist care (n=22).

Potential study limitations: cannot exclude the possibility that some patients may have been attending hepatology clinics outside St Mary's Hospital, this information was not documented in notes.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Length of follow-up	Outcome measures	Source of funding
Taylor 2010	Cross-sectional survey (abstract) Study quality: Inadequate information on recruitment Poor response rate (28%) Small sample size	N=45 45/161 questionnaires were completed and returned.	Recruitment/setting: Department of Gastroenterology, Queen Elizabeth Hospital, London, UK Aim: to assess GP knowledge on HBV. Source of data: A survey containing 32 questions was sent to GPs within the catchment area. Another questionnaire was sent again if there was no response after several months. Exclusion: Not stated. Baseline characteristics Mean age, years: 46 Duration worked at GP, years (range): 14 (1-35) Practice contains >5,000 patients, %: 96%	Not applicable	GP knowledge Proportion (%) of those who knew how to correctly screen for HBV Proportion (%) of those who would refer patients to a specialist	Not stated

Results

90% (n=41/45) of respondents would attend an education session on viral hepatitis.

36% (n=16/45) of GPs thought all patients with CHB should be managed in secondary care

Outcome	n/N (%)
Proportion of GPs who knew how to correctly screen for HBV	8/45 (17%)

Two scenarios for HBV were presented:

A pregnant woman found to be HBsAg positive on screening;

A Nigerian man known to be HBsAg positive, who had an ALT 4 x ULN

Scenarios	Proportion of those who would refer patients to a specialist, n/N (%)
A pregnant woman found to be HBsAg positive on screening	24/45 (53%)
A Nigerian man known to be HBsAg positive, who had an ALT 4 x ULN	16/45 (36%)

Author's conclusion: Without a basic understanding of chronic viral hepatitis, including when to refer, a significant proportion of patients will not receive appropriate treatment. Improved training and education are required for GPs and hospitals should provide clear management guidelines to local GPs.

E.3 Referral Thresholds

<table>
<tr><th>Bibliographic reference</th><th>Study type/ Study quality</th><th>Number of patients</th><th>Patient characteristics</th><th>Prognostic factor(s)</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Chu 2007</td><td>Prospective follow up study</td><td>N=133</td><td>HBeAg positive patients with normal ALT level (0-36 U/L), no evidence of cirrhosis based on clinical grounds and liver ultrasonography and no concomitant infection with hepatitis C or delta at the baseline and no antiviral therapy before entry or during follow up who had documented seroconversion from HBeAg to anti-HBe.
Baseline characteristics
<table>
<tr><td></td><td>Total (n=133)</td><td>Men (n=75)</td><td>Women (n=58)</td></tr>
<tr><td>Mean age on entry in years (SD)</td><td>28.2 (6.9)</td><td>28.3 (6.4)</td><td>28.2 (7.5)</td></tr>
<tr><td>Genotype
-B
-C</td><td>
108 (81%)
25 (19%)</td><td>
64(85%)
11(15%)</td><td>
44(76%)
14(24%)</td></tr>
<tr><td>Interval from entry to HbeAg seroconversion (years)</td><td>4.6 (3.7)</td><td>4.6 (4.0)</td><td>4.5 (3.3)</td></tr>
<tr><td>Follow up duration following HbeAg seroconversion (years)</td><td>5.8 (4.2)</td><td>5.9 (4.3)</td><td>5.7 (4.1)</td></tr>
</table>
</td><td>Maximal ALT during HBeAg positive phase (immune clearance phase)</td><td>For a minimum of 1 year following HBeAg seroconversion</td><td>Reactivation of hepatitis B defined as raise to more than twice the ULN of ALT levels, accompanied by positive serum HBV DNA (>1.4 X 105 copies/ml) by hybridization assays.</td><td>By a grant from National Science of Council of Taiwan.</td></tr>
<tr><td colspan="8">Results:</td></tr>
</table>

The annual rate of reactivation of hepatitis B was 3.3%.

The cumulative probabilities of reactivation of hepatitis B were 15.1%, 29.8% and 32.8% respectively after 5, 10 and 15 years of follow up.

Predictive models for reactivation of hepatitis B following HbeAg seroconversion

	Univariate analysis*		Multivariable analysis*▪	
Prognostic factors	Hazard ratio (95% C.I)	P value	Hazard ratio (95% C.I)	P value
Maximal ALT during HbeAg positive (immuno clearance) phase <2 x ULN 2-5 x ULN >5 x ULN	 1 (0.72-6.16) 3.01 (1.12-8.08)	 0.17 0.029	 1 (0.89-8.47) 3.57 (1.22-10.46)	 0.08 0.02

* Cox proportional hazards regression models.

▪ Multivariable analysis included the following predictive factors: age on entry, gender, genotype, interval from entry to HbeAg seroconverion (in years) and age at HbeAg seroconversion.

The authors concluded that ALT levels>5 x ULN during the HbeAg positive phase was correlated significantly with reactivation of hepatitis B after HbeAg seroconversion.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Lai 2007A	Retrospective	N=192 Initial N= 593 401 excluded	Recruitment/setting: screened the charts of all patients seen in the Beth Israel Deaconess Medical Center Liver Center (USA) between Jan 2000 and April 2005. Inclusion: HBsAg positive, HBV DNA ≥10,000 copies/mL, a liver biopsy or clinical cirrhosis.	Based on pre-biopsy ALT values, patients were classified into 1 of the 3 categories*: 1.Persistently	N/A	Significant fibrosis or inflammation (by METAVIR scoring) Significant fibrosis (stage 2-4)	Not stated

Exclusion: patients with hepatocellular carcinoma, immunosuppression, HIV, history of positive HCV RNA, hemachromatosis or other chronic liver disease or treatment with oral antiviral nucleos(t)ides therapy prior to biopsy, but included if their therapy was limited to IFN more than 1 year prior to biopsy.

Baseline characteristics

	Normal ALT	1-1.5xULN	>1.5xULN
Sex M/F, n (%)	24 (41)/35 (59)	16 (62)/10 (38)	89 (83)/18 (17)
Prior treatment with IFN, n (%)	2 (3)	1 (4)	5 (5)
Race White Black Asian Hispanic	 4(7) 6 (10) 49 (84) -	 3(12) 3(12) 20 (77) -	 29 (27) 10 (9) 66 (62) 2 (2)
HBeAg (+), (%)	56	38	63
Mean age, 95% CI	37 (33-40)	39 (35-44)	40 (37-43)
Mean weight (kg), 95% CI	64.3 (60.1-68.5)	67.3 (61.8-72.7)	72.5 (69.1-75.9)

normal ALT (n=59)
2.ALT 1-1.5x ULN (n=26)
3.ALT>1.5xULN (n=107)

*maximal ALT level over > min. 6 months determined the group selection.

Normal ALT – defined as having at least 2 ALT values ≤40IU/L at least 6 months apart and no elevated ALT at any time point prior to biopsy, for both men and women

No significant fibrosis (stage 0-1)

Significant inflammation (grade 2-3)
No significant inflammation (stage 0-1)

			Mean log viral load, 95% CI	6.3 (5.9-6.8)	6.1 (5.5-6.7)	6.6 (6.4-6.9)			
			Mean (95%CI) Stage Grade	 0.7 (0.4-1.0) 1.3 (1.2-1.5)	 1.4 (0.8-1.9) 1.5 (1.3-1.8)	 2.1 (1.8-2.4) 2.0 (1.8-2.1)			

Results:

Overall 37% patients in the normal ALT group had either significant inflammation or fibrosis.

Stage of fibrosis or grade of inflammation by ALT

	Significant fibrosis (F2-4)	Significant inflammation (A2-3)
Normal ALT	18%	34%
1-1.5xULN	34%	54%
>1.5xULN	62%	78%

Patients with persistently normal ALT levels were further categorised as low normal (0-25 IU/L) (n=20) and high normal (26-40 IU/L) (n=39).

Overall 20% of patients with low normal ALT had either significant inflammation or fibrosis.

Stage of fibrosis or grade of inflammation by normal ALT subgroups

	Significant fibrosis (F2-4)	Significant inflammation (A2-3)
Low normal (0-25)	5%	20%
High normal (26-40)	25%	41%

ALT groups were stratified into subgroups: <1x, >1x, >1.5x, >2x, >3x and >5x ULN; the distribution of stage and grade was not statistically significantly different between the different high ALT groups.

Prediction of significant fibrosis and inflammation results, based on multivariable logistic regression controlling for all covariates, including race, sex, prior treatment with IFN, viral load, weight, age, eAg positivity

Sig. fibrosis	Adjusted OR (95% CI)	P values
Age		0.0005

≤40 >40	1.0 1.08 (1.03-1.13)	
ALT group Normal ALT High ALT (≥1xULN)	 1.0 1.58 (1.03-2.44)	 <0.0001
Sig. inflammation		
ALT group Normal ALT High ALT (≥1xULN)	 1.0 2.01 (1.29-3.15)	 0.002

Prediction of significant fibrosis and inflammation results stratified by HBeAg status, based on multivariable logistic regression controlling for all covariates, including race, sex, prior treatment with IFN, viral load, weight, age, eAg positivity

	Sig. fibrosis	Adjusted OR (95% CI)	P values
Age	HBeAg (+) (N= ≤40 >40 HBeAg (-) ≤40 >40	 1.0 1.07 (1.01-1.14) 1.0 1.10 (1.02-1.18)	 0.017 0.0165
ALT group	HBeAg (+) Normal ALT High ALT (≥1xULN) HBeAg (-) Normal ALT High ALT (≥1xULN)	 1.0 1.77 (1.02-3.07) -	 0.04
	Sig. inflammation		
ALT group	HBeAg (+) Normal ALT High ALT (≥1xULN)	 1.0 1.89 (1.08-3.29)	 0.026

	HBeAg (-) Normal ALT High ALT (≥1xULN)	-	

Increasing ALT was not a predictor of significant fibrosis and inflammation in HBeAg (-) patients (data not shown).

Study limitations: inability to characterise the upper limit of viral replications in all subjects. The PCR assays used in this study did not dilute serum to quantify the upper end and so the range stopped at >200,000 copies/mL for many patients

Only patients with HBV DNA >10,000 copies/mL were biopsied so cannot comment on patients with even lower HBV DNA levels.

Referral bias – cannot exclude that only the sicker population was being referred.

Author's conclusion: results suggest that clinicians need to evaluate all patients with HBV DNA >10,000 copies/mL carefully for liver fibrosis and inflammation and that age >40y and an ALT >25 (high normal) may trigger evaluation with a liver biopsy.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Chen 2010B	Retrospective	N=228 Chinese patients	Recruitment/setting: patients from the centre of infections diseases, West China were screen between Aug 2006 and Jan 2008 Inclusion: HBsAg positive for at least 6 months prior to liver biopsy; no present or past evidence of any symptoms related to liver disease; no prior treatment with an anti-viral agent such as IFN and NUCs. Exclusion: Co-infection with HCV, HEV, or HIV; any rising of ALT that is more than 2xULN Baseline characteristics	ALT groups 1.Normal ALT (≤1xULN) 2.Slightly elevated ALT (>1xULN but <2xULN) HBV DNA groups 1.<100,000 copies/mL 2.≥100,000 copies/mL	N/A	Significant fibrosis (stage ≥2) or inflammation (grade ≥2) (by Scheuer scoring) A professional pathologist assessed all biopsy samples.	Not stated

	All	Normal ALT	>1.xULN
N	228	141	87

Male, n (%)	128 (56.1)	82 (58.2)	46 (52.9)
Age (mean±SD)	32.5±9.6	33±10.1	31.7±8.7
BMI (mean±SD)	21.7±2.8	21.5±2.7	21.9±2.8
Positive family history (%)	144 (63.4)	91 (64.5)	54 (62.1)

	HBVDNA <100,000	≥100,000
N	109	119
Male, n (%)	69 (63.3)	59 (49.6)
Age (mean±SD)	34.6±9.9	30.6±9
BMI (mean±SD)	21.6±2.6	21.7±2.6
Positive family history (%)	69 (63.3)	76 (63.9)

	HBeAg (+)	HBeAg (-)
N	104	124
Male, n (%)	54 (51.9)	74 (59.7)
Age (mean±SD)	33.9±9.7	30.9±9.3
BMI (mean±SD)	21.9±2.7	21.3±2.9
Positive family	80 (64.5)	65 (62.5)

			history (%)								

Results:

Stage of fibrosis or grade of inflammation by ALT levels

	Significant fibrosis (stage ≥2)	Significant inflammation (grade ≥2)
Normal ALT (≤1xULN) (n=141)	47 (33.3%)	67 (47.5%)
Slightly elevated ALT (>1xULN but <2xULN) (n=187)	77 (41.4%)	97 (51.7%)

The frequency of inflammation and fibrosis was similar in these two groups (p=0.586 and 0.22, respectively)

Stage of fibrosis or grade of inflammation according to HBV DNA levels

	Significant fibrosis (stage ≥2)	Significant inflammation (grade ≥2)
<100,000 copies/mL (n=109)	56 (51.4%)	46 (42.2%)
>100,000 copies/mL (n=119)	56 (47.1%)	37 (31.1%)

The frequency of inflammation and fibrosis was similar in these two groups (p=0.515 and 0.082, respectively)

Stage of fibrosis or grade of inflammation according to age

Age	Significant fibrosis (stage ≥2)	Significant inflammation (grade ≥2)
≤29y (n=88)	18.2%	34.1%
30-40y (n=88)	39.8%	46.6%
>40y (n=52)	61.5%	78.8%

Significant trend for fibrosis to be more common in older patients (p<0.001).

Prediction of significant fibrosis and inflammation results, based on multivariable logistic regression controlling for all covariates, including age, ALT, HBeAg status, HBV DNA, family history)

Sig. inflammation	Adjusted OR (95% CI)	P values
Age Less advanced More advanced	0.51 (0.34-0.76)	0.001

ALT group	0.88 (0.48-1.60)	0.669
Sig. fibrosis		
Age Less advanced More advanced	0.48 (0.32-0.73)	0.001
ALT group	0.64 (0.34-1.21)	0.172

Author's conclusion: many Chinese patients with CHB and ALT<2xULN have histologically significant liver damage, and that the incidence of significant inflammation and fibrosis was greater in older patients. Liver biopsy is needed in these patients to assess the need for anti-viral treatment.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Nakazawa 2011	Prospective	N=104 Initial N = 136	Recruitment/setting: consecutively enrolled at the asymptomatic CHB carrier clinic between Feb 1995 and June 2007; Japan Inclusion: (HBsAg positive) HBeAg negative, HBeAb positive patients with normal ALT level (<40IU/L) for at least 6 months as confirmed by >2 exams before enrolment; did not habitually drink alcohol; no previous or ongoing antiviral treatment for seroconversion; negative for antibodies for HCV and HIV; no findings of fatty liver or liver cancer Exclusion: as above. Baseline characteristics (N=104) Age (years): 49±11 (22-74) N male/female: 56/48	ALT HBV DNA	Mean 6.4±3.4 years (1-14.3)	Hepatic reactivation (≥60IU/L) (at least >1.5 x ULN)* *definition used in this study was slightly lower than that used in previous studies as patients who habitually drank alcohol and those with fatty liver were excluded.	Health and Labour Sciences Research Grants for research on intractable diseases from Ministry of Health, Labour and Welfare of Japan

Family history (%)	43 (41)
ALT (IU/L)	21±8 (8-39)
Platelet (104/mm3)	20.7±5.3 (10.1-45.8)
HBV DNA, log10 copies/mL, n (%) <2.6 2.6-<3 3-<4 4-<5 5-<6 ≥6	 26 9 30 28 7 4
Genotype, n A B C	 4 24 74
Precore mutant, n	77

Results:

During follow up, hepatitis reactivation occurred in 14 patients (13.5%).

The mean time from enrolment to hepatitis reactivation was 1.9±1.5 years.

The cumulative rates of hepatitis reactivation were 13.7% at 5 years and 15.5% at 10 years.

Predictive value of ALT and HBV DNA for future hepatitis reactivation

	Hazard ratio (95%CI)	P value
ALT (IU/L) ≤20 (n=60) 21-40 (n=44)	 1.0 18.43 (2.38-142.7)	 <0.005
HBV DNA (log10 copies/mL) <5 (n=93) ≥5 (n=11)	 1.0 3.43 (1.14-10.31)	 0.028

The 10y cumulative rate of future hepatitis reactivation was 49.1% among carriers with HBV DNA ≥5 log10 copies/mL, when compared with 11.2% among those with lower levels.
The 10y cumulative rate of future hepatitis reactivation was 35.8% among carriers with ALT 20-<40 IU/L, when compared with 1.9% among those with lower levels.

Author's conclusion: an HBV DNA level of ≥5log10 copies/mL predicts subsequent hepatitis reactivation in HBeAg negative carrier with persistently normal ALT. As the baseline HBV DNA reflects the future level, appropriate clinical management according to the viral level is expected to decrease future risk.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Kumar 2008	Prospective	N=1387 HBeAg (+) N=603 HBeAg (-) N=784	Recruitment/setting: liver clinic, dep, of gastroenterology, G.B. Pant Hospital India between Jan 1996 and June 2005. HBsAg positivity detected through blood donation screening, routine check up, family screening. Inclusion: asymptomatic HBsAg positive patients for at least 6 months; no present or past evidence of any symptoms related to liver disease; at least 2 visits and follow up of ≥12 months; 2 or more ALT values Exclusion: HCV, HDV, HIV, decompensated liver disease, evidence of liver disease because of other aetiology, use of hepatotoxic drugs Baseline characteristics HBeAg (+) <table><tr><td></td><td><40IU/L Persistently normal ALT (N=73)</td><td>>40IU/L Persistently or intermittently high ALT (N=530)</td></tr><tr><td>Male, n (%)</td><td>63 (86.3)</td><td>456 (86)</td></tr></table>	ALT groups 1.Persistently normal ALT (≤40IU/L) (n=189) 2.Persistently * or intermittently ** elevated ALT (>40IU/L) (n=1198) *all 3 ALT values had remained >40IU/L until start of treatment/last follow up **at least 1 >40IU/L in	≥1 year	Significant fibrosis or inflammation (by Knodell index)	Not stated

			Age (y), mean±SD	27.7±15.3	31.4±15.6	previous 1 year prior to baseline biopsy or anytime until start of treatment/last follow up.		
			BMI, mean±SD >25, n (%) >30, n (%)	 12 (16.4) 10 (13.7)	 100 (18.9) 58 (10.9)			
			Histological grade*, median (range)	5 (1-11)	5 (1-16)			
			HAI >3, n (%)	46 (63)	400 (78.7)			
			Histologic stage, median *(range)	1 (0-4)	2 (0-4)			
			Distribution of fibrosis stage: 0/1/2/3/4*	17.8/42.5/26/ 11/2.7	5.3/29.5/41.7/ 16.6/6.9			
			Baseline HBV DNA*, log copies/ml, median (range)	5.23 (2.78-9.27)	6.19 (2.82-11.81)			
			Genotype*, (%) A C D A+D	 8.2 0 83.6 8.2	 30 2.5 62.3 5.2			
			*p=<0.01 HBeAg (-)					
				<40IU/L Persistently normal ALT	>40IU/L Persistently or intermittently			

	(N=116)	high ALT (N=668)
Male, n (%)	79 (68.1)	535 (80.1)
Age (y), mean±SD	34.6±14.5	33.6±14.2
BMI, mean±SD >25, n (%) >30, n (%)	 21 (18.1) 14 (12.1)	 155 (23.2) 85 (12.7)
Histological grade*, median (range)	3(1-10)	7 (1-15)
HAI >3*, n (%)	23 (39.7)	512 (80.8)
Histologic stage*, median (range)	1 (0-3)	2 (0-4)
Distribution of fibrosis stage: 0/1/2/3/4	39.7/46.6/8.6/ 5.2/0	6.3/29.8/43.5/ 14.2/6.2
Baseline HBV DNA*, log copies/ml, median (range)	4.29 (2.78-9.2)	5.78 (2.78-9.41)
Genotype, (%) A C D A+D	 30.2 0 60.3 9.5	 35.1 1.1 56.2 7.6
Precore mutant, m		

			(%)	44 (37.9)	268 (40.1)			
			*p=<0.001					

Results:

Baseline HBV DNA levels

Distribution of HBV DNA in HBeAg (+) patients

	Persistenly normal ALT (<40 IU/L)	Persistently/intermittently elevated ALT (>40IU/L)	P value	Persistently normal ALT, according to the updated AASLD cut-off criteria (Men 30IU/L Women 19IU/L)
Median HBV DNA (log copies), range	5.23 (2.78-9.27)	6.19 (2.82-11.81)	0.013	5.29 (2.83-9.26)
HBV DNA ≥100,000 copies/mL, n (%) 10,000-<100,000 1000-<10,000 <1000	 44 (60.3) 14 (19) 10 (14) 5 (7)	 391 (73.8) 122 (23) 14 (3) 3 (1)	 0.018 0.001 0.001 0.001	18 (66.7)

Distribution of HBV DNA in HBeAg (-) patients

	Persistently normal ALT (<40 IU/L)	Persistently/intermittently elevated ALT (>40IU/L)	P value	Persistently normal ALT, according to the updated AASLD cut-off criteria (Men 30IU/L Women 19IU/L)
Median HBV DNA (log copies), range	4.29 (2.78-9.2)	5.78 (2.78-9.41)	≤0.001	4.38 (2.78-9.2)
HBV DNA ≥100,000 copies/mL, n (%) 10,000-<100,000 1000-<10,000	 41 (35.3) 23 (20) 23 (20)	 508 (76) 98 (15) 24 (4)	 ≤0.001 0.001 0.001	19 (41.3)

<1000	29 (25)	38 (6)	0.001	

Distribution of fibrosis stages in HBeAg positive and negative patients

HBeAg (+)	Persistently normal ALT (<40 IU/L) (n=73)	Persistently/intermittently elevated ALT (>40IU/L) (n=508)	P value	Persistently normal ALT, according to the updated AASLD cut-off criteria (Men 30IU/L Women 19IU/L)
Median HAI, range	5 (1-11)	5 (1-16)	0.009	5 (2-11)
Median fibrosis score, range	1 (0-4)	2.0 (0-4)	<0.001	1 (0-4)
F≥2 F<2	29 (39.7) 44 (60.3)	331 (65.1) 177 (34.9)	≤0.001	Not given
HBeAg (-)	(n=58)	(n=634)		(n=26)
Median HAI, range	3 (1-10)	7 (1-15)	<0.001	3 (1-81)
Median fibrosis score, range	1 (0-3)	2 (0-4)	<0.001	1 (0-2)
F≥2 F<2	8 (13.8) 50 (86.2)	405 (63.9) 229 (36.1)	<0.001	5 (19.2) 9+12= 21 (80.8)

Multiple logistic regression for prediction of significant fibrosis (Adjustment factors not given by paper)

Sig. fibrosis (F≥2)	Adjusted OR (95% CI)	P values
Baseline HBV DNA <10,000 copies ≥10,000 copies	 1.0 1.859 (1.18-2.92)	 0.007
ALT group <40IU/L persistently normal >40IU/L persistently/ intermittently elevated	 1.0 4.3 (2.87-6.45)	 <0.001

Age, y		
<30	1	
30-39	0.93 (0.698-1.25)	0.64
40-49	1.13 (0.82-1.57)	0.447
≥50	1.66 (1.13-2.45)	0.01

Subgroup analysis

Frequency of fibrosis according to HBV DNA level in HBeAg negative patients with persistently normal ALT and persistently normal ALT (updated definitions)

HBeAg (-)	HBV DNA <5 log copies		HBV DNA <4 log copies	
	<40IU/L	M: <30IU/L F: <19IU/L	<40IU/L	M: <30IU/L F: <19IU/L
n with liver biopsy	29	12	9	4
Any fibrosis, n (%)	15 (51.7)	8 (66.7)	6 (66.7)	2 (50)
Inactive liver disease (HAI <3 and fibrosis stage ≤1), n (%)	23 (79.3)	9 (75)	7 (77.8)	3 (75)
Active liver disease (HAI ≥3 and fibrosis stage ≥2), n (%)	6 (20.7)	3 (25)	2 (22.2)	1 (25)

Author's conclusion: A fair proportion of CHB patients with persistently normal ALT have HBV DNA ≥5log copies/mL and significant fibrosis. Use of ALT and HBV DNA levels without resorting to liver biopsy to define "inactive carrier state" in HBeAg (-) persistently normal ALT patients may miss histologically significant disease in a proportion of patients.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Chu 2010	Retrospective	N=250	Recruitment/setting: asymptomatic adults who were identified incidentally (consecutively) as	HBV DNA (COBAS	N/A	Active hepatitis (HBsAg positive,	Not stated

			HBsAg carriers during blood donation or health checkups received regular clinic follow up evaluation at the carrier clinic between Jan 2007 and Dec 2007, Taiwan Inclusion: asymptomatic CHB patients: HBsAg positive, HBeAg negative, anti-HBe positive, persistently normal ALT (≤36 U/L) at least once every 6-12 months for at least 10 years until the last visit; no evidence of cirrhosis or hepatocellular carcinoma based on clinical assessment and liver ultasonographic findings; no concomitant infection with HCV or HDV; no antiviral or immunomodulatory therapy before enrolment. Exclusion: asymptomatic CHB: patients who underwent HBsAg seroclearance during the follow up period. Baseline characteristics – inactive carriers Overall (N=250): M/F ratio 84:166; Age at baseline, y (mean±SD) 34.4±8.8; Duration of persistently normal ALT levels before enrolment, y (mean±SD) 16.1±4.7; No. of ALT determinations before	amplicator HBV monitor test, Roche diagnostics) Lowest limit of detection = 200 copies/mL		HBeAg negative, anti-HBe positive, persistently abnormal ALT 2xULN, HBV DNA>104 copies/mL)	

			enrolment				
			Maximal ALT levels before enrolment, U/L ≤19 20-30 30-36	 26(10) 159(64) 65(26)			
			Age at enrolment, y	50.6±9.6			
			ALT levels were sig. higher in male carriers than female carriers. A total of 52 male carriers and 23 female carriers had persistently normal ALT levels according to the strict criteria of ALT of 30U/L or less in males and 19U/L or less in females.				

Results:

HBV DNA levels in inactive carriers with persistently normal ALT levels

	Overall (≤36U/L)	Subset of patients with ALT <30U/L and <19U/L in men and women, respectively
HBV DNA (log10 copies/mL)	n/250 (%)	n/75 (%)
<2.3 (undetectable)	43 (17)	9 (12)
2.3-2.99	28 (11)	8 (7)
3-3.99	89 (36)	26 (35)
4-4.99	65 (26)	24 (32)
5-5.99	25 (10)	8 (11)
Median (range)	3.7 (<2.3-5.98)	3.81 <2.3-5.45)

No significant difference in HBV DNA between males and females.

Predictive factors for active infection in anti-HBe positive carriers with HBV DNA>104 copies/mL (multiple logistic regression)

N=90	OR (95%CI)	P value
HBV DNA 104-105 copies/mL >105 copies/mL	 1.0 21.5 (8.4-55.4)	 <0.0001
Sex Female Male	 1.0 8.2 (3.4-20.0)_	 <0.001

Study limitations: no stored serum available for testing HBV DNA levels at baseline/before enrolment. No histological exam or fibroscan to exclude significant liver disease in the inactive carrier population.

Author's conclusion: Nearly 40% of inactive carriers had HBV DNA levels of 104 copies/mL or greater. Female sex, HBV DNA levels of 104 to 105 copies/mL, correlated with inactive carrier state.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Papatheodoridis 2008A	Retrospective	N=434 399 with elevated ALT on ≥2 occasions and any level of detectable HBV DNA 35 inactive carrier with persistently normal ALT	Recruitment/setting: Sept 2001 and Dec 2007, Greece Inclusion: treatment naïve HBeAg negative CHB patients who underwent liver biopsy at two hospitals. HBsAg positive and HBeAg negative for at least 6 months and detectable HBV DNA. The inclusion of patients with elevated ALT and normal ALT ended in Aug 2007 and Dec 2007. No patient received antiviral or immunosuppressive therapy during the study period. Exclusion: HDV, HCV, HIV coinfection; those with decompensated liver disease and/or hepatocellular carcinoma at presentation. Baseline characteristics Group A = DNA ≥200,000 IU/mL	HBV DNA using PCR assay (Roche) (lowest limit of detection = 400copies/ mL)	N/A	Histological indication for treatment = grading score ≥7 and/or stage ≥2, according to the Ishak scoring system.	Not stated

		and HBV DNA 2000 and 20000IU/mL	Group B = DNA 20,000-<200,000 IU/mL Group C = DNA 2,000-<20,000 IU/mL Group D = DNA 80-<2,000 IU/mL					All liver biopsies were evaluated by a single liver histopathologist who was blind to the ALT values and serum HBV DNA levels.

	Group A N=203	Group B N=91	Group C N=63	Group D N=42
Age, years	49±13	51±14	48±15	43±15
Male, (%)	156 (77)	71 (78)	48 (76)	35 (83)
BMI, kg/m2	26±4	26±4	25±3	26±5
Alcohol abuse	15 (7)	6 (7)	4 (6)	0
ALT, U/L	121 (12-784)	75 (14-656)	61 (12-387)	52 (13-565)
Normal ALT	18 (9)	14 (15)	15 (24)	12 (29)
AST, U/L	78 (18-592)	66 (20-449)	41 (15-222)	38 (16-242)
Fibrosis No/mild (0-1) Moderate (2-3) Severe (4) Cirrhosis (5-6)	3.3±1.5 23 (11) 99 (49) 28 (14) 53 (26)	3.4±1.9 17 (19) 29 (32) 12 (13) 33 (36)	2.8±1.7 16 (25) 24(38) 10(16) 13(21)	2.2±1.71 7 (40) 17(40) 3(7) 5(12)

Inactive carriers

	HBV DNA 2,000-<20,000 IU/mL N=35

Age, years	43±13
Male, (%)	22(63)
BMI, kg/m2	25±3
Alcohol abuse	2(7)
ALT, U/L	28(13-39)
Normal ALT	35(100)
AST, U/L	23(16-40)
Fibrosis No/mild (0-1) Moderate (2-3) Severe (4) Cirrhosis (5-6)	1±0.6 29(83) 6(17) 0 0

Results:

Proportion of patients with histological indication for treatment (n, %)

HBV DNA (IU/mL)	HBeAg negative patients (with elevated ALT ≥2 occasions, any level of detectable HBV DNA) (n=399)	Inactive carriers (persistently normal ALT for ≥12mo and HBV DNA <20,000IU/mL) (n=35)
>200,000	203 (50.9)	--
20,000-<200,000	91 (22.8)	--
2,000-<20,000		29/35 (82.9)

	63 (15.8)	
<2,000	42 (10.5)	--

Risk factors associate with presence of histological indication for treatment (Ishak grading score ≥7 and/or stage ≥2), based on multivariable logistic regression analysis

OR(95%CI); p value	All patients (HBeAg negative + inactive carriers) (N=434)	HBeAg negative patients (N=399)
On liver biopsy		
Normal ALT	1.0	1.0
Abnormal ALT	3.7 (2.0-6.6); p=<0.001	2.1 (1.1-4.2); p=0.037
Age, years		
<30	1.0 (p for trend = <0.001)	1.0 (p for trend=<0.001)
30-44	2.7 (1.3-5.9); p=0.01	2.9 (1.3-6.4); p=0.008
45-59	8.0 (3.4 (18.4); p=<0.001	10.5 (4.3-25.8); p=<0.001
≥60	15.6 (5.6-43.5); p=<0.001	20.5 (6.6-63.4); p=<0.01
Serum HBV DNA, IU/mL		
80-<2000	1.0 (p for trend =<0.001)	1.0 (p for trend = <0.001)
2000-<20,000	1.7 (0.7-4.2); p=0.266	1.6 (0.6-4.2); p=0.30
20,000-<200,000	2.2 (0.9-5.5); p=0.08	2.2 (0.9-5.4); p=0.098
≥200,000	5.5 (2.4-13.0); p=<0.001	4.9 (2.0-11.6);p=<0.001

Author's conclusion: HBeAg negative CHB patients with persistently or transiently increased ALT and HBV DNA ≥20,000IU/mL almost always require therapeutic intervention, but histological indications for treatment are also present in the majority of such cases with HBV DNA<20,000 and even <2000 IU/mL. Minimal histological lesions are observed in the majority of HBeAg negative patients with persistently normal ALT and HBV DNA >2000 IU/mL, who may not require immediate liver biopsy and treatment but only close follow up.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-	Outcome measures	Source of funding

					up		
Lin 2007A	Prospective	N=414	Recruitment/setting: patients were consecutively enrolled; Taiwan Inclusion: HBeAg negative/anti-HBe-positive carriers with persistently normal ALT for at least 2 years in periodic biochemical exams before enrolment. Exclusion: coinfections with HCV, HDV, HIV; antiviral treatment before and during follow up period Baseline characteristics	HBV DNA -real time PCR (detection limit = 100 copies/mL)	N/A	High normal ALT (0.5-1xULN) (ULN = 40IU/L and 30 IU/L for men and women)	Grant from the Taipei City Hospital and the Department of Health and the National Science Council

	Overall (n=414)	Low normal (n=176)	High normal (n=238)
Age (years, mean±SD)*	39±10	37±10	41±10
Sex M/F, n (%)	229(55.3) / 185(44.7)	94(53.4)/ 82(46.6)	135(56.7)/ 103(43.3)
ALT*	20±8	13±4	25±6
HBV DNA			
Detectable	353(85.3)	153(86.9)	200(84)
Undetectable	61(14.7)	23(13.1)	38(16)
Log10 copies*	4.7±1.5	4.3±1.4	5±1.5
<4			
4-5	122(34.6)	70(45.8)	52(26)
5-6	100(28.3)	38(24.8)	62(31)
6-7	74(21)	28(18.3)	46(23)
≥7	37(10.5)	14(9.2)	23(11.5)
	20(5.7)	3(2)	17(8.5)

			Genotype B C	 276(78.2) 77(21.8)	 120(78.4) 33(1.6)	 156(78) 44(22)	
			Precore mutant	252(71.4)	104(68)	148(74)	

*p=≤0.001

Results:

37.2% of HBeAg negative carriers with persistently normal ALT had an HBV DNA >105 copies/mL.

Multiple logistic regression analysis of factors associated with high-normal ALT level

	OR (95%CI)	P value
HBV DNA level <4log10 ≥4log10	 1.0 1.83 (1.07-3.13)	 0.62
Age, years <30 30-39 40-49 ≥50	 1.0 2.43(1.18-5.03) 4.22(1.99-8.93) 4.06(1.69-9.78)	 0.016 <0.001 0.002 0.027
Sex Female Male	 1.0 1.82 (1.10-3.01)	 0.019

Author's conclusion: HBeAg negative patients with persistently normal ALT are not a homogeneous group, and those with high-normal ALT share some of the characteristics that have been associated with adverse long-term outcomes.

Bibliographic	Study type/	Number	Patient characteristics	Prognostic	Length	Outcome	Source of

<table>
<tr><th>reference</th><th>Study quality</th><th>of patients</th><th></th><th>factor(s)</th><th>of follow-up</th><th>measures</th><th>funding</th></tr>
<tr><td>Montazeri 2010</td><td>Prospective</td><td>N=132</td><td>Recruitment/setting: Iran

Inclusion: asymptomatic HBsAg carriers with persistently normal ALT (<40IU/L) for 12 months; age between 16-70y, HBeAg negative, anti-HBe positive

Exclusion: co-infection with HCV, HDV, HIV; chronic liver disease due to other causes.
Baseline characteristics
<table>
<tr><th></th><th>Normal ALT</th><th>1-1.5xULN</th><th>>1.5xULN</th></tr>
<tr><td>Sex M/F, n (%)</td><td>24 (41)/35 (59)</td><td>16 (62)/10 (38)</td><td>89 (83)/18 (17)</td></tr>
<tr><td>Prior treatment with IFN, n (%)</td><td>2 (3)</td><td>1 (4)</td><td>5 (5)</td></tr>
<tr><td>Race
White
Black
Asian
Hispanic</td><td>
4(7)
6 (10)
49 (84)
-</td><td>
3(12)
3(12)
20 (77)
-</td><td>
29 (27)
10 (9)
66 (62)
2 (2)</td></tr>
<tr><td>HBeAg (+), (%)</td><td>56</td><td>38</td><td>63</td></tr>
<tr><td>Mean age, 95% CI</td><td>37 (33-40)</td><td>39 (35-44)</td><td>40 (37-43)</td></tr>
<tr><td>Mean</td><td>64.3 (60.1-</td><td>67.3 (61.8-</td><td>72.5</td></tr>
</table></td><td>HBV DNA
(real time PCR with the lowest limit of detection of 5.8IU/mL).

ALT</td><td>Followed each 3 months after baseline liver biopsy. 61 patients agreed to have the second liver biopsy.</td><td>Histological disease – total HAI score (≥5), fibrosis stage (≥2), necro-inflammatory grade (≥4), according to the Knodell scoring system.

All liver biopsies were reviewed by a single pathologist who was blinded to the clinical data.</td><td>Grant from the Digestive Disease Research Centre, Tehran University of Medical Sciences, Iran</td></tr>
</table>

			weight (kg), 95% CI	68.5)	72.7)	(69.1-75.9)			
			Mean log viral load, 95% CI	6.3 (5.9-6.8)	6.1 (5.5-6.7)	6.6 (6.4-6.9)			
			Mean (95%CI) Stage Grade	 0.7 (0.4-1.0) 1.3 (1.2-1.5)	 1.4 (0.8-1.9) 1.5 (1.3-1.8)	 2.1 (1.8-2.4) 2.0 (1.8-2.1)			

Results:

Multivariable binary regression analysis of effect of factors on histological disease (based on the Knodell scoring system)

	Multivariable OR (unless specified) (95%CI)*		
	Total score (HAI) ≥5	Necroinflammation (grade ≥4)	Fibrosis (stage≥2)
HBV DNA (log10 IU/mL) <2.9 (4467 copies) ≥2.9	 1.0 5.43 (2.4-12.3); p=<0.0001	 1.0 3.47 (1.58-7.47); p=0.02	 1.0 4.23(1.81-9.85); p=<0.0001
ALT (IU/L) <23 ≥23	Univariate 1.0 1.10(0.5-2.2); p=0.86	Univariate 1.0 1.03(0.51-2.08); p=1.00	Univariate 1.0 1.95(0.91-4.14); p=0.09
Gender Female Male	 1.0 2.2(0.98-4.93); p=0.055	 1.0 2.47(1.13-5.4); p=0.02	 1.0 1.35(0.60-3.02);p=0.46
Age (years) <36 ≥36	 1.0 1.98(0.89-4.38); p=0.09	 1.0 2.2 (1.03-4.86); p=0.04	 1.0 1.52(0.62-3.4);p=0.30

*median values were chosen as cut off values.

Author's conclusion: HBeAg negative CHB infection with persistently normal ALT is not a silent disease.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Seo 2005	Retrospective	N=64	Recruitment/setting: Japan Inclusion: Patients with chronic HBV infection seen between 1989 and 2002 Exclusion: none stated. Baseline characteristics HBeAg (+) or (-): "Group C": 12 persistently normal ALT (HBeAg negative carriers) + "Group D": 10 persistently normal ALT (seroconversion); Elevated ALT: "Group A": 18 persistent elevation (9 HBeAg + and 9 HBeAg-); "Group B": 24 intermittent elevation (7 HBeAg + and 17 HBeAg-) Sex M/F, n: Group C 5 male, ; Group A: 12	HBV DNA (Amplicot HBV Monitor Test with the lowest limit of detection of 2.6 log copies/mL and highest 7.6log copies).	Mean 51.5 months (range 5-157 months)	Not stated how patients classified into groups	not stated

			(%)	7 female; group D 6 male 4 female	male, 6 female; group B 14 male, 10 female				
			Mean (SD) age (yr)	C: 45.3 (15.5); D: 37.0 (14.1)	A: 42.5 (10.9); B: 42.9 (8.7)				
			Weight	not stated	not stated				
			Mean (SD) log copies/mL viral load	C: 3.5 (1.1); D: 3.7 (1.0)	A: 5.9 (1.7); B: 5.5 (1.6)				

Results:

Phase	Group A (persistent elevation ALT)	Group B (intermittent elevation ALT	Group C (HBeAg- and Normal ALT)	Group D (sustained HBeAg seroconversion and normal ALT)	Total
Immune tolerant (HBeAg +)	-	-	-	-	-
Immune active (HBeAg +)	9	7			16
Inactive carrier (HBeAg -)	-	-	12	10	**22**
Reactivation (HBeAg -)	9	17	-	-	**26**
Total	18	24	12	10	64

The study compared HBV-DNA levels between HBeAg - inactive carriers (n=22) and HBeAg – "chronic hepatitis" (i.e. reactivation) patients (n=26)

For a one-off measure of HBV-DNA level: Mean (SD) 3.6 (1.0) log copies/mL for **Inactive carriers (HBeAg-)** and 4.8 (1.5) for **Reactivation (HBeAg-)** p<0.005

Percentage of patients with HBV-DNA above this cut-off score:	**Inactive carrier (HBeAg-) n=22**	**Reactivation (HBeAg-) n=26**
>3.0	68%	96%
>4.0	32%	50%
>4.5	23%	50%
>5.0	18%	45%

>5.5	9%	32%
>6.0	0	14%
>6.5	0	13%
>7.0	0	12%

For HBV-DNA measured twice (in a subset of 24 patients): Mean (SD) 3.2 (0.9) for **Inactive carriers (HBeAg-)** vs. 5.5 (1.3) log copies/mL **Reactivation (HBeAg -)**, p<0.001

Percentage of patients with HBV-DNA above this cut-off score:	**Inactive carrier (HBeAg-) n=10**	**Reactivation (HBeAg-) n=14**
>4.5	20%	71.4%
>5.0	10%	71.4%
>5.5	0	57.1%
>6.0	0	35.7%

If testing is performed twice with a 4-month interval, the cut-off value of 10^5 copies/mL would misclassify 10% of inactive carriers and 28.6% of patients with reactivation.

Author's conclusion: It is not possible to define a single cut-off for differentiating inactive carriers from patients with reactivated chronic hepatitis B; however, a cut off of 10^5 copies/mL is appropriate.

Bibliographic reference	**Study type/ Study quality**	**Number of patients**	**Patient characteristics**	**Prognostic factor(s)**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Lee 2011	Retrospective	N=136	Recruitment/setting: Taiwan Inclusion: Treatment-naive patients (none received	HBV DNA (Cobas Amplicor HBV	Liver biopsy at same	Significant fibrosis (defined as ≥2 on Ishak scoring	National Science Council,

			anti-viral treatment [nucleoside/nucleotide analogues or interferon] before liver biopsy) with chronic HBV infection (HBsAg +); negative for HBeAg for at least 6 months; elevated serum ALT (≥40U/L, 1 x ULN) recorded at least 1 month apart, HBV DNA >2000 IU/mL Exclusion: HCV, hepatitis D or HIV co-infection; anti-nuclear antibody titre ≥1:160; positive test for anti-smooth muscle antibody or anti-mitochondrial antibody; use of hepatotoxic drugs or Chinese herb; alcoholic liver disease; radiologic evidence (ultrasound, CT or MRI) of hepato-cellular carcinoma. Baseline characteristics: see table below	Monitor Test with the lowest limit of detection of 12IU/mL). ALT (systemic multi-auto-analyzer)	time as biochem istry	system Significant inflammation (Ishak grade ≥7)	Taipei Veterans General Hospital, Taipei, Taiwan

Baseline characteristics:

	No significant fibrosis n=72	Significant fibrosis n=64	p value	No sig. inflammtion (grade <7) n=101	Significant inflammation (grade ≥7) n=35	p value
Mean (SD) age (yr)	48.1 (11.6)	54.0 (12.6)	p=0.003	48.8 (12.2)	56.8 (11.1)	p=0.001
Sex (% male)	55/72 (76.4%) male	44/64 (68.8%) male	NS	74/101 (73.3%) male	25/35 (71.4%) male	NS
BMI kg/m^2)	24.75 (2.92)	25.35 (3.11)	NS	24.77 (3.15)	25.79 (2.46)	NS
Type 2 diabetes	4/72 (5.6%)	13/64 (20.3%)	p=0.019	10/101 (9.9%)	7/35 (20%)	NS
ALT (U/L)	114 (18-1434)	150 (43-2390)	p=0.017	111 (18-1510)	189 (72-2390)	p<0.001
AST (U/L)	63 (16-1084)	92 (19-1400)	p=0.004	62 (16-1160)	140 (39-1400)	p<0.001
Total bilirubin (mg/dL)	0.73 (0.19 to 1.9)	0.7 (0.17-10)	NS	0.7 (0.17 to 1.9)	0.84 (0.32-10)	NS
Prothrombin time (INR)	1.006 (0.066)	1.045 (0.074)	p=0.003	1.010 (0.653)	1.067 (0.077)	p<0.001
WBC (/cumm)	5934 (1485)	5935 (1682)	NS	6132 (1492)	5365 (1688)	p=0.007
Hb (g/dL)	14.32 (1.47)	13.91 (1.72)	NS	14.22 (1.62)	13.86 (1.51)	NS
Platelet (x 10^9/L)	203 (59.86)	168 (43.27)	p<0.001	198 (55.22)	154 (41.60)	p<0.001

Creatinine (mg/dL)	0.922 (0.239)	0.899 (0.232)	NS	0.90 (0.230)	0.92 (0.252)	NS
HBV DNA (IU/mL)	1.08 x 10^6 (2014-6.56 x 10^9)	1.09 x 10^6 (2500-1.38 x 10^9)	NS	6.03 x 10^5 (2014-6.56 x 10^9)	3.4 x 10^6 (2500-4.98 x 10^8)	p=0.016

Results:

Factors associated with hepatic fibrosis and necro-inflammation by multivariate analysis

Variable	p value	Odds ratio	95% Confidence interval
Hepatic fibrosis (Ishak stage ≥2)			
BMI ≥25kg/m^2	0.001	3.758	1.665 – 8.483
AST >40U/l	0.001	9.172	2.388 – 35.226
HBV DNA >20,000 IU/mL	0.012	4.596	1.392 – 15.172
Platelet <150 x 10^9/L	0.026	2.839	1.131 – 7.126
Hepatic necro-inflammation			
BMI ≥23kg/m^2	0.005	7.359	1.841 – 29.420
ALT >80U/l	0.033	9.920	1.205 – 81.634
HBV DNA >10^9 IU/mL	0.014	3.212	1.263 – 8.168
Platelet <150 x 10^9/L	0.005	3.881	1.497 – 10.062

Author's conclusion: BMI and HBV viral loads may have synergistic effects on disease progression in HBeAg-negative CHB. Both controlling body weight and anti-viral therapy are important in the management of CHB.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Malik 2011	Cross-	N=140	Recruitment/setting: UK	HBV DNA	Liver	Significant fibrosis	none stated

	sectional		Inclusion: Adult treatment-naive patients with chronic HBV infection (HBsAg + for >6 months) Exclusion: none stated Baseline characteristics: n: 140 Mean (SD) age (years): 39.5 (13.4) Male: 84 (60%) HBeAG positive: 56 (40%) HBeAg negative: 84 (60%) Caucasian: 76 (54%) Asian: 45 (32%) Afro-Caribbean: 19 (14%) Serum ALT (IU/L): 86.6 (53) Platelet count: Normal (245 +/-23) Serum bilirubin: Normal (15µmol/L) INR: Normal (1) Albumin: Normal (40g/L) Liver biopsy length (cm): 3.4 (1.1) Ishak necro-inflammatory score: 4.0 (2) Fibrosis score: 2.8 (1.8)	(copies/mL measured by ABBOTT real-time quantitative PCR and ABI PRISM). ALT (method not stated)	biopsy at same time as biochemistry	(modified Ishak scoring system: 0-2 defined as mild disease, 3-4 moderate disease, 5-6 severe disease) Significant inflammation (Ishak grade >3; 0-3 defined as mild inflammation)	

Results:

	65 HBeAG + patients					84 HBeAG - patients				
ALT category	Total number of	HBV DNA copies/mL:	Necro-inflammat	Mild fibrosis	Moderate/ severe	Total no. of	HBV DNA copies/mL:	Necro-inflammat	Mild fibrosis	Moderate/ severe

	patients	no. of patients	ory score	(no. of patients)	fibrosis (no. of patients)	patients	no. of patients	ory score	(no. of patients)	fibrosis (no. of patients)
<20	8	>6 log: 8	1 (1.5)	8	0	1	<3 log: 1 pt <3-6 log: 0 >6 log: 0	1	1	0
20-30	6	>6 log: 6	2.4 (2.1)	4	2	13	<3 log: 12 <3-6 log: 1 >6 log: 0	3.0 (1)	10	3
31-40	11	>6 log: 11	3.7 (2.3)	6	5	15	<3 log: 12 <3-6 log: 3 >6 log: 0	3.5 (1.5)	8	7
41-80	16	>6 log: 16	4 (2.5)	8	8	37	<3 log: 18 <3-6 log: 11 >6 log: 8	3.8 (2.5)	14	23
>80	15	>6 log: 15	5 (2.5)	5	10	18	<3 log: 5 <3-6 log: 3 >6 log: 10	5.5 (1.5)	6	12

Multivariate analysis: factors associated with moderate/severe liver fibrosis

	Variable	Univariate analysis: significant at p<0.05?	Multivariate analysis: significant at p<0.05?
Age	>45 Years	Yes	Yes (p=0.045)
Gender	Male	No	No
Ethnic grop	Asian/Afro-Caribbean	Yes	Yes (p=0.02)
Viral load	HBV DNA level >6 log	Yes	No
Serum ALT	ALT >40	No	No
Hepatic inflammation	Necro-inflammatory score >3	Yes	No

Author's conclusion: HBeAg status, age, ethnic group with longitudinal assessment of LFTs and viral load should be studies in patients with "normal ALT" at the upper end of the normal range (20-40 IU/L) to appropriately classify patients and identify patients for liver fibrosis assessment to inform treatment decisions.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Göbel 2011	Retrospective	N=253	Recruitment/setting: Germany Inclusion: Adult treatment-naive patients with chronic HBV infection (HBsAg + for >6 months) Exclusion: Acute hepatitis B, coinfection with HCV, HDV or HIV Baseline characteristics: n: 253 Mean (SD) age (years): 40 (14) Male: 184/253 (73%) HBeAG positive: 103/253 (41%) HBeAg negative: 150 (59%) Caucasian: 208/253 (82%) Asian/African: 45 (18%) Serum ALT (IU/L): 80 (154) Duration of diagnosis of HBV prior to biopsy (yr): 6 (8) AST (U/L): 46 (70)	ALT (method not stated; normal range <23 U/L males and 19 U/L females)	Liver biopsy at same time as biochemistry	Significant fibrosis (Desmet/Scheuer score ≥F2) Significant inflammation (grade ≥G2) Both on routine diagnostic biopsy	none stated

GGT (U/L)	46 (59)
HBV DNA (log IU/mL)	7.39 (7.98)
No viraemia (no. of patients)	46/253 (18%)
HBV genotype: A B C D other	 52/154 (34%) 5/154 (3%) 15/154 (10%) 76/154 (49%) 6/154 (4%)
Mean (SD) histological stage	1.9 (1.3)
Significant liver fibrosis	134/253 (53%)
Liver cirrhosis	51/253 (20%)
Histologic grade (mean +/- range)	1.7 (0.7)
Significant liver inflammation	114/253 (55%)

Results:

	ALT ≤ ULN (n=39)	ALT 1-2 ULN (n=86)	ALT >2 ULN (n=128)	p value
Significant liver fibrosis	14/39 (36%)	44/86 (51%)	76/128 (59%)	0.02
Significant liver inflammation (grade only available for 208 patients)	8/30 (27%)	37/73 (51%)	69/105 (66%)	0.002

	<40 years	≥40 years	p value
Significant liver fibrosis: All patients Elevated ALT Normal ALT	 51/130 (39%) 45/110 (41%) 6/20 (30%)	 83/123 (67%) 75/104 (72%) 8/19 (42%)	 <0.001 <0.001 NS
Significant liver inflammation: All patients	 52/112 (46%)	 62/96 (65%)	 0.009

Elevated ALT	49/98 (50%)	57/80 (71%)	0.004
Normal ALT	3/14 (21%)	5/16 (31%)	NS

Main focus of paper was uni- and multivariate analysis of factors associated with cirrhosis (which was not associated with ALT level).

Author's conclusion: In a European setting, patients with chronic hepatitis B and normal transaminases often have significant liver fibrosis or cirrhosis. Therefore, liver biopsy or liver stiffness measurement should be performed in these patients to determine the stage of liver fibrosis.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Zheng 2012	Cross-sectional	N=13637 people without risk factors for liver disease (derivation cohort for new definition of ULN ALT) Same	Recruitment/setting: China Inclusion: 13637 people without risk factors for liver disease (derivation cohort for new definition of ULN ALT at 95th percentile in this population) aged 19-44 years Same 13637 people without risk factors for liver disease plus 3523 people with chronic hepatitis B plus 5598 with non-alcoholic fatty liver disease (NAFLD) to look at sensitivity/specificity of new cut-off Exclusion: People drinking alcohol >40g/day for men and >20g/day for women; those taking any of 168 listed medications or 50 herbs known to be associated with hepatotoxicity; overweight	ALT (Hitachi 7600 automatic analyzer)	Diagnosis of CHB known at same time as biochemistry	Prediction of chronic hepatitis B status	National Science and Technology Major Project of China, Scientific Research Foundation of Wenzhou, Zhejiang Province, China, Health Bureau of Zhejiang

		13637 people plus 3523 people with chronic hepatitis B plus 5598 with non-alcoholic fatty liver disease (NAFLD)	(>25kg/m^2 for both genders); missing fasting laboratory data; hypertriglyceridaemia (≥1.7mmol/L), low HDL-C (<1.03mmol/L for men and <1.29 mmol/L for women), impaired fasting plasma glucose (FPG; ≥5.6mmol/L) elevated blood pressure (≥130/85mmHg) or hyperuricaemia (>420µmol/L for men and >360µmol/L for women). The normal group also had to have absence of fatty liver by ultrasound, absence of known chronic liver disease and normal laboratory values (biochemistry, HBsAg negative, HCV antibody negative, HIV antibody negative) Baseline characteristics:				Province, Research Foundation ofEducation Bureau of Zhejiang Province and Project of New Century 551 Talent Nurturing in Wenzhou.

13637 people without risk factors for liver disease	Men (n=4765)	Women (n=8872)
Mean (95% CI) age (years)	33.3 (33.1-33.4)	34.4 (34.2-34.5)
Mean (95% CI) BMI kg/m^2	21.13 (21.08-21.19)	20.39 (20.35-20.43)
Mean (95% CI) systolic BP mmHg	109.8 (109.7-110.1)	104.1 (103.9-104.3)
Mean (95% CI) diastolic BP mmHg	73.4 (73.3-73.6)	69.6 (69.4-69.7)
Mean (95% CI) total cholesterol mmol/L	4.55 (4.51-4.60)	4.56 (4.53-4.59)
Mean (95% CI) triglycerides mmol/L	0.96 (0.95-0.97)	0.73 (0.72-0.74)

			Mean (95% CI) HDL-C mmol/L	1.48 (1.39-1.59)	1.89 (1.64-2.23)			
			Mean (95% CI) LDL-C mmol/L	2.83 (2.77-2.92)	2.57 (2.55-2.60)			
			Mean (95% CI) fasting plasma glucose (FPG) mmol/L	5.10 (5.08-5.11)	5.04 (5.03-5.05)			
			Mean (95% CI) uric acid mmol/L	360.6 (358.3-362.8)	263.8 (262.6-265.1)			
			Mean (95% CI) ALT IU/L	16.5 (16.1-16.8)	12.2 (12.0-12.5)			

Results:

Defining the new upper limit of normal in the group (n=13637) without risk factors for liver disease: 95th percentile of ALT 35.2 U/L in men and 23.4 U/L in women. These values used as the new upper limits of normal in the next part of the study.

	Proportion of patients with chronic hepatitis B with "raised" ALT using different cut off values for the upper limit of the normal range		Sensitivity (95% CI)		Specificity	
	Men	Women	Men	Women	Men	Women
Using old cut-off value (55 IU/L for both men and women)	844/2278 (37.1%)	143/1245 (11.5%)	15.84 (14.2-17.7)	6.61 (5.3-8.2)	98.68 (98.3-99.0)	99.39 (99.2-99.5)
Using newly defined cut off value (35.2 U/L in men and 23.4 U/L in women)	1055/2278 (46.3%)	444/1245 (35.7%)	39.35 (37.0-41.7)	35.27 (32.6-38.0)	94.84 (94.2-95.4)	94.61 (94.1-95.1)

Concordance statistics for detection of liver disease in HBV: 0.873 (95% CI 0.865-0.881) in men and 0.857 (95% CI 0.850-0.864) for women

Author's conclusion: The previous ULN for ALT is set too high to reliably detect chronic liver disease in China. The updated upper limit of ALT of 35 U/L for men and 23 U/L for women in Chinese Han population allows greater sensitivity in diagnosing early liver disease.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Park 2012B	Prospective	N=104	Recruitment/setting: Korea Inclusion: Adult treatment-naive patients with chronic HBV infection (HBsAg + for >6 months); HBeAg negative/anti-HBe positive, HBV genotype C, normal ALT (≤40 IU/mL) for ≥12 months, HBV viral loads <2000 IU/mL for ≥12 months Exclusion: Coinfection with HCV, HDV or HIV, underlying decompensated cirrhosis, or hepatocellular carcinoma Baseline characteristics: n: 104 Median (range) age (years): 49 (23-75) ale: 65 (62.5%) HBeAg positive: 0 HBeAg negative: 104	HBV DNA by real-time PCR assay on a COBAS TaqMan 48 analyzer with a detection limit of 12 IU/mL Serum HBsAg using ARCHITECT HBsAg QT immunoassay	Median 39 (range 36-42) months	Reactivation of HBV replication	Korea Healthcare Technology R&D project, Ministry of Health and Welfare, Republic of Korea

Median (range) HBV DNA (log IU/mL)	2.25 (1.08-3.33)
Median (range) serum ALT (IU/L)	25 (8-40)
Median (range) AST (U/L)	22 (13-40)
Median (range) total bilirubin (mg/dL)	0.9 (0.4-3.7)
Median (range) alkaline phosphatase (IU/L)	66 (35-171)
Median (range) platelet count 10^6/µL	189 (49-591)
Median (range) prothrombin time (INR)	1.00 (0.82-1.78)
Median (range) HBsAg (IU/mL)	1043.90 (0.56-32200)
Median (range) HBsAg ($\log_{10}$ IU/mL)	3.02 (-0.25 to +4.51)
Cirrhosis	34 (32.7%)
Fibroscan (kPa) (meaningful cirrhosis value on Fibroscan = >10.1kPa)	7.95 (3.20-39.70)
Genotype C	104 (100%)

Results:

At the end of follow up, patients were classified into: inactive carriers (consistently had HBV DNA levels <2000 IU/mL and ALT ≤ 40 IU/mL during follow up, n=73; and HBeAg negative chronic hepatitis (reactivation) whose HBV DNA or ALT levels had ever exceeded the previous standards, n=31.

Variables (median [range] or n [%]) unless stated otherwise	Inactive carriers (n=73)	HBeAg negative chronic hepatitis (reactivation) n=31	p value	Multivariate analysis	p value
Age (years)	49 (23-75)	47 (27-66)	0.768		
Gender (male)	44 (60.3%)	21 (67.7%)	0.472		
HBV DNA ($\log_{10}$ IU/mL)	1.89 (1.08-3.33)	3.12 (1.42-3.29)	p<0.001	OR 14.902 (95% CI 5.001-44.408)	p<0.001

ALT (IU/L)	24 (8-40)	25 (11-40)	0.752		
AST (IU/L)	22 (13-40)	29 (14-39)	0.368		
Total bilirubin (mg/dL)	0.9 (0.4-3.7)	0.8 (0.4-1.5)	0.598		
Platelet count 10^6/µL	198 (49-591)	172 (74-350)	0.355		
Alkaline phosphatase (IU/L)	62 (35-171)	71 (40-142)	0.279		
Prothrombin time (INR)	1.00 (0.82-1.78)	1.00 (0.90-1.12	0.427		
HBsAg ($\log_{10}$ IU/mL)	2.78 (-0.25 to + 4.51)	3.28 (2.25-4.35)	p=0.001	OR 5.512 (95% CI 1.615-18.806)	p=0.006
Cirrhosis	20 (27.4%)	14 (45.2%)	0.077		
Fibroscan (kPa)	7.95 (4.10-39.70)	7.90 (3.20-26.30)	0.658		
Follow up period (months)	39 (36-42)	39 (38-40)	0.174		

Prediction of hepatitis B reactivation

	HBsAg >850 IU/mL	HBsAg >850 IU/mL and HBV DNA > 850 IU/mL	HBV DNA > 850 IU/mL
Sensitivity (%)	83.9	64.5	74.2
Specificity (%)	54.8	93.2	84.9
Positive predictive value (%)	44.1	80.0	67.6
Negative predictive value (%)	88.9	86.1	88.6
Diagnostic accuracy (%)	63.5	84.6	81.7

Author's conclusion: Although it is inferior ot other genotypes and to serum HBV DNA alone, single point HBsAg level has a favourable diagnostic accuracy in genotype C HBeAg negative HBV carriers and is expected to provide additional information for managing chronic hepatitis B.

E.4 Diagnostics

Author, year	Study type	Number of patients/ number excluded from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Other index tests - how is it measured? - index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Zhu 2011	Cross-sectional	175 Consecutive patients _____ 3 patients (1.7%) excluded because LSM was not successful due to a high BMI (>30) in two patients, a narrow inter-costal space in one	Recruitment/setting/Country: West China hospital Inclusion: adult patients with clinically diagnosed chronic HBV infection (HBeAg positive and negative) who underwent percutaneous liver biopsy from March 2009 to April 2010. Exclusion: chronic liver disease due to other causes, e.g. coinfection with HIV, HCV, HDV; alcohol intake >40g/day, non-alcoholic steatohepatitis, autoimmune hepatitis, primary biliary cirrhosis, and decompensated liver cirrhosis. Patients with ALT >2xULN Baseline characteristics Male, n (%): 137 (78.3)	Liver stiffness measurement (LSM) using transient elastography (Fibroscan) All patients underwent 2 sets of LSM within 24 hour of liver biopsy. LSMs were assessed by two independent, trained operators who were blinded to each other's results and to other	APRI Patients received comprehensive clinical and lab assessments within 7 days of liver biopsy Calculation: [(AST/ULN) / platelet count (109/L)] x 100	Liver biopsy Performed using a 16-gauge needle using the standard Menghini technique. Liver histology was assessed by a pathologist blinded to other data.	Specimens were graded for fibrosis according to METAVIR classification Significant liver fibrosis, defined as fibrosis score 2-3 Liver cirrhosis, defined as fibrosis	Sensitivity Specifivity PPV NPV, using cut offs according to original studies AUC Optimal cut off values were chosen based on	The National Key Technologies Research and Development Program of China, national S&T Major project for infectious diseases

		patient.	Age (years), mean ±SD (range): 36.5 ±9.4 (17-69) Biochemical parameters, mean ±SD (range) ALT (U/L): 40.1 ± 18.6 (7-103) AST (U/L): 36.1 ± 17.1 (12-53) Albumin (g/L): 45.9 ± 4.3 (26-73) Albumin/globulin: 1.6 ±0.3 (0.7-2.4) WBC x 109/L: 5.5 ± 1.5 (2.9-10.8) Platelet x 109/L: 132.4 ± 52.8 (30-353) HBeAg (+): 85 (48.6) (-): 90 (51.4) METAVIR stage (%) F0-1: 96 (54.9) F2-3: 50 (28.6) F4: 29 (16.6)	measurements ≥10 valid LSM values were acquired for each patient, and median LSM was calculated. Measurements with a success rate of <60% were deemed as failures and the median LSM with IQR >30% median values were excluded from analysis. The final LSM value was the average of the median LSM values obtained by 2 operators.			score 4	a max. sum of sensitivity and specificity	control, national basic research program of China

Results

	Significant fibrosis (F2-3)*		Cirrhosis (F4)**	
	LSM	APRI	LSM	APRI

Optimal cut off value	>7.9 kPa	>0.5	>13.8 kPa	>1.0
AUC (95% CI)	0.95 (0.91-0.98)	0.81 (0.74-0.87)	0.98 (0.96-0.99)	0.83 (0.77-0.90)
Sensitivity (%)	88	82	93.1	75.9
Specificity (%)	90.6	83.3	91.1	69.2
Positive predictive value (%)	83	71.9	67.5	32.8
Negative predictive value (%)	93.5	89.9	98.5	93.5

*compared to fibrosis score F0-1

**compared to fibrosis score F0-3

2x2 table

Significant fibrosis

Index tests	Reference standard (liver biopsy)	
	Sig. fibrosis (F2-3) (n=50)	No sig. fibrosis (F0-1) (n=96)
LSM (fibroscan)		
7.9-13.8 kPa (n=53)	44	9
<7.9 kPa (n=93)	6	87
APRI		
0.5-1.0 (n=57)	41	16
<0.5 (n=89)	9	80

Cirrhosis

Index tests	Reference standard (liver biopsy)	
	Cirrhosis (F4) (n=29)	No cirrhosis (F0-3) (n=146)
LSM (fibroscan)		
≥13.8 kPa (n=40)	27	13
<13.8 kPa (n=135)	2	133
APRI		
≥1.0 (n=67)	22	45
<1.0 (n=108)	7	101

LSM (Fibroscan) has the higher performance for detection of significant fibrosis or cirrhosis, compared to APRI.

Author's conclusion: TE is a reliable predictor of significant fibrosis and cirrhosis in Western Chinese patients with chronic HBV infection, and is superior to APRI, FS cut off values could be considered as clinical reference for detecting significant fibrosis and cirrhosis.

Author, year	Study type	Number of patients/ no. excluded from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Marcellin 2009A	Cross-sectional cohort	202 consecutive patients _____ 15 (7.4%) had a non-interpretable LB; 14 (6.9%) had an LSM considered as	Recruitment/setting/Country: France, 5 difference hospitals Inclusion: HBsAg positive, HBV DNA >105 copies/mL and liver histology compatible with chronic hepatitis. Exclusion: patients with chronic alcohol intake or HCV coinfection and patients with ascites. Baseline characteristics Male, n (%): 115 (66.5) Age (years), mean ±SD: 40.1 ±12.8	Liver stiffness measurement (LSM) using transient elastography (Fibroscan) LSM was performed within 3 months of the liver biopsy. Several successful acquisitions were performed on each patient.	Liver biopsy All biopsy specimens were analysed by two experienced pathologists blinded to the results of LSM and clinical data. Liver biopsies that	METAVIR and Ishak score Significant fibrosis: F2-4 vs. F0-1 Severe fibrosis: F3-4 vs. F0-2 Cirrhosis: F4 vs. F0-3	AUC and its 95% CI (Mann-Whitney) Sensitivity Specificity PPV, NPV Likelihood ratio according to optimal cut	Not stated

		unreliable (9 of them had a BMI >25) 173 patients were included in the analysis	Biochemical parameters, median (range) ALT (IU/L) AST (IU/L) Albumin (g/L) Platelet x 103/mm3 Prothrombin time (% of normal) Total bilirubin (µM/L) Gamma-globulin (g/L)	 54 (30-85) 35 (25-54) 44.5 (42-47.4) 207 (156-235) 90 (81-98) 11 (8-14) 13.8 (11-16.7)	Success rate was calculated as the ratio of the no. of successful acquisitions over the total no. of acquisitions. Median value was kept as representative of the liver elastic modulus. Only results of LSM obtained with ≥7 successful acquisitions and success rate of ≥50% were considered reliable. Blood parameters were evaluated on the same day that LSM was performed.	contained <10 portal tracts (except for cirrhosis) were excluded from the histological analysis. Fibrosis stage was assessed independently on each histological section by both pathologists.		offs. Optimal cut off values were defined using different criteria: 1) Maximising the sum of sensitivity and specificity 2) maximising the diagnostic accuracy (% patients diagnosed correctly)	
			Mean BMI (kg/m2) ± SD	24.5 ±4.0				
			METAVIR stage (%) 0 1 2 3 4	 16 (9.2) 70 (40.5) 44 (25.4) 29 (16.8) 14 (8.1)				
			Ishak 0 1 2 3 4 5 6	 14 (8.1) 41 (23.7) 39 (22.5) 34 (19.7) 17 (9.8) 14 (8.1) 14 (8.1)				

Results

TE

	Significant fibrosis (F2-4 vs. F0-1)	Severe fibrosis (F3-4 vs. F0-2)	Cirrhosis (F4 vs. F0-3)
AUC (95% CI)	0.81 (0.73-0.86)	0.93 (0.88-0.96)	0.93 (0.82-0.98)

Optimal cut off values according to different optimum criteria

Maximum of sensitivity + specificity	Significant fibrosis	Severe fibrosis	Cirrhosis
Optimal cut off (kPa)	7.2	8.1	11
Sensitivity	70	86	93
Specifivity	83	85	87
PPV	80	65	38
NPV	73	95	99
Likelihood ratio	4.0	5.6	7.0
Diagnostic accuracy	76	85	87
Maximum of diagnostic accuracy			
Optimal cut off (kPa)	7.2	10.5	18.2
Sensitivity	70	72	57
Specifivity	83	95	97
PPV	80	84	67
NPV	73	91	96
Likelihood ratio	4.0	15.6	22.7
Diagnostic accuracy	76	90	94

Additional results: no significant difference was observed between smaller and larger LBs (keeping the breakdown of the population according to fibrosis stage) for AUCs. No significant difference was observed between the two pathologists for AUCs.

Author's conclusion: LSM (Fibroscan) appears to be reliable for detection of significant fibrosis or cirrhosis in HBV patients and cut off values are only slightly

different from those observed in HCV patients.

Notes: 173 patients were included in the analysis, of whom 8 had daily alcohol intake ≥40g, 2 had HDV coinfection and 11 had HIV coinfection.
Most (93%) of the 173 patients included in the analysis had LB and LSM within the same day or the day after (mean delay: 2±9 days; success rate was 90 ±14%.
LSM was not recordable in 6.9% (mainly due to overweight), comparable to the % patients with non-interpretable LB (7.4%).

Author, year	Study type	Number of patients / no. exclude from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Other index tests - how is it measured? - index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes Loss to follow up	Source of funding
Myers 2003	Retrospective and cross-sectional	209 _____ 223 patients met the inclusion criteria; 14 were excluded due to immunosuppression, concomi	Recruitment/setting/Country: France Inclusion: HIV negative patients with CHB Exclusion: Concomitant liver diseases (except HDV) and immunosuppression. Baseline characteristics (all patients*) Male, n (%): 147 (70) Age (years), median (IQR): 39 (32-50) African (%): 129 (62)	Fibrotest (including total bilirubin, GGT, α2-macroglobulin, apolipoprotein A1, haptoglobin, corrected for age and gender) Retrospective	Actitest (also including ALT) for activity Higher scores indicates a greater chance of significant lesions	Liver biopsy Single blinded pathologist analysed the biopsies using METAVIR classification	METAVIR Fibrosis: F2-4 vs. F0-1 Necoinflammatory activity: A2-3 vs. A0-1 A0 no activity	AUC and its 95% CI (Mann-Whitney) Sensitivity Specificity PPV, NPV Likelihood ratio	The Canadian association for the study of the liver, Schering Canada, the Royal College of Physicians and Surgeons of Canada, Canadian

		tant liver diseases (n=2) and incomplete biochemical data (n=1).	Asian Caucasian HBV status (%) HBeAg (+) HBV DNA (+) HDV coinfection Biochemical parameters, median (IQR) ALT (IU/L) AST (IU/L) GGT (g/l) α2-macroglobulin (g/l) apolipoprotein A1 (g/l) haptoglobin (g/l) Total bilirubin (µM/L) Fibrosis stage (%) F0 (no fibrosis) F1 F2 F3 F4 (cirrhosis) Necroinflammatory activity (%) A0 (none) A1 A2 A3 (severe) *Differences between retrospective group and cross-sectional group were not	47 (23) 33 (16) 35 (17) 145 (69) 19 (9) 41 (27-70) 32 (25-48) 26 (17-52) 2.01 (1.64-2.54) 1.38 (1.18-1.57) 0.79 (0.42-1.15) 9 (7-13) 76 (36) 72 934) 32 (15) 10 (5) 19 (9) 83 (40) 85 (41) 36 (17) 5 (2)	group: patients biopsied between 1997 and 2001 with serum collected within 6 months of the biopsy. Cross-sectional group: patients biopsied between 1997 and 2002; assays were performed on fresh serum. Median interval between serum sample collection and liver biopsy: 1 day (range: 110 days before to 181 days after). 95% of samples were within 3 months of the biopsy; 81% within 1 month; 78%	(range 0-1)		A1 mild activity A2 moderate activity A3 severe activity	A priori sensitivity analyses according to ethnicity (African vs. non African), HBV DNA positivity, HDV coinfection	Institutes for Health Research, the Alberta heritage foundation for Medical research, the association pour la Recherche sur le Cancer and the association de Recherche sur les Maladies Hepatiques Virales.

			statistically significant, except for % HBV DNA (+) patients was slightly higher in the cross-sectional group (p=0.04).	within 10 days.					

Results

AUC of Actitest for prediction of necroinflammatory activity (A2-3 vs. A0-1) = 0.82 ± 0.04

Sensitivity analyses showed that ethnicity, HBV DNA positivity, and HDV coinfection did not affect its accuracy. However, AUC tends to be lower in HBeAg (+) patients (but this is not statistically significant, p=0.21):

AUC for HBeAg (+) (n=35): 0.71±0.09

AUC for HBeAg (-) (n=174): 0.84±0.05

AUC of Fibrotest for prediction of fibrosis (F2-4 vs. F0-1)= 0.78 ± 0.04

Sensitivity analyses showed that HBV DNA positivity, and HDV coinfection did not affect its accuracy. However, AUC tends to be lower in HBeAg (-) patients (p=0.07):

AUC for HBeAg (+) (n=35): 0.89±0.06

AUC for HBeAg (-) (n=174): 0.76±0.05

Diagnostic values of Fibrotest for predicting F2-4 fibrosis*

	Fibrosis (F2-4 vs. F0-1)				
Cut off values	0.20	0.40	0.60	0.80	0.90
Sensitivity	89	54	34	18	8
Specifivity	52	80	93	99	100
PPV	43	53	68	92	100
NPV	92	81	78	75	73
Positive likelihood ratio	1.85	2.76	5.1	26.7	-

*Prevalence of F2-4 fibrosis, 29% (61/209). Sensitivity and PPV refer to values above the cut-off, specificity and NPV refer to values less than or equal to the cut-off.

If LB was restricted to patients with intermediate Fibrotest scores (>0.20 and ≤0.80), the index could have prevented 46% (96/209) of biopsies, while maintaining 92%

accuracy (88/96)

Using this strategy, 7/84 patients with a Fibrotest ≤0.20 would have been misclassified as having F0-1 fibrosis (all had F2 fibrosis). Conversely, 1/12 patients with Fibrotest scores >0.80 would have been misclassified as having F2-4 fibrosis.

Author's conclusion: Fibrotest appears useful for the identification of HBV related fibrosis, and Actitest appears useful for excluding significant necroinflammation.

Notes:

Patients were not studied consecutively but according to individual physician practice because these markers were not routinely assessed. This could have introduced selection bias (the retrospective population was selected predominantly on the basis of the availability of stored serum rather than clinical characteristics.

Because baseline characteristics did not differ significantly between the retrospective and the cross-sectional group, they were analysed together as one group of patients.

Fibrotest and Actitest were also compared to AST and ALT alone, this data are not extracted (tests not included in the protocol).

Other potential study limitations: majority of the population were African and HBeAg (-) – results may not be applicable to other countries with a different population. Time interval between serum sample and LB could be up to 6 months (although 95% of samples were within 3 months of the biopsy; 81% within 1 month; 78% within 10 days), this may have introduced bias due to spontaneous changes in HBV-related histological lesions.

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Other index tests - how is it measured? - index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Lesmana 2011	Cross-sectional Sample size	117 consecutive patients	Recruitment/setting/Country: 2 hospitals in Indonesia Inclusion: CHB patients intending to initiate treatment.	Liver stiffness measurement using transient	APRI LFT was performed by an	Liver biopsy Performed by senior pathologist,	METAVIR Significant fibrosis: F2-4 vs. F0-1	AUC* and its 95% CI *AUC was adjusted	

	calculation provided		Exclusion: ALT levels >5xULN (ALT flares) or patients with acute exacerbation. Baseline characteristics F0-1 (n=44) / F2-4 (n=73) Age (years), mean ±SD: 41.5±11.17 / 40.1±10.9 Male (%): 63 (53.8) Biochemical parameters, mean±SD ALT (U/L)*: 31.9±19.5 / 57.1±41.7 AST (U/L)*: 28±13.2 / 45.2±29.9 Albumin (g/dL): 4.4±0.34 / 4.3±0.34 Platelet x 109/ml: 257.5± 68.3 / 252.5± 62.5 Total bilirubin (mg/dL): 0.8±0.36 / 0.8±0.45 HBV DNA (log10 copies/ml)*: 5.2±1.96 / 6.5±2.03 Mean BMI (kg/m2) ± SD: 23.2±3.54 / 23.2±3.42 HBeAg status Positive (%)*: 13 (29.5) / 42 (57.5) Negative (%): 31 (70.5) / 31 (42.5) Fibrosis stage (%): All patients (n=117) 0: 3 (2.6)	elastography (TE) (Fibroscan) Measurements were performed on the same day with liver biopsy. 10 successful measurements performed on each patient. Success rate = no. validated measurements/ total no. measurements. Median value of successful measurements was taken (IQR<30% of median and success rate >60%)	automated blood analyser Unclear when blood markers were taken OR Combination of TF and APRI	blinded to patient's clinical history. Adequate specimens, ≥15mm long and contains 5 portal systems.	Severe fibrosis: F3-4 vs. F0-2	(due to skewed data) according to the prevalence of fibrosis stages using the difference between advanced and non-advanced fibrosis Sensitivity Specificity PPV, NPV Likelihood ratio Cut off values selected by maximising the sum of sensitivity and specificity.	

1	41 (35)
2	45 (38.5)
3	24 (20.5)
4	4 (3.4)

*p value<0.005

Results

	Significant fibrosis (F2-4 vs. F0-1)			Severe fibrosis (F3-4 vs. F0-2)		
	TE	APRI	TE + APRI	TE	APRI	TE +APRI
Cut off	5.85 kPa	0.235		7 kPa	0.27	
Sensitivity (%)	60.3	64.4	67.1	65.5	72.4	72.4
Specificity (%)	63.6	70.5	61.4	80.7	71.6	71.6
PPV	73.3	78.3	74.2	52.8	45.7	45.7
NPV	49.1	54.4	52.9	87.7	88.7	88.7
LR +	1.66	2.18	1.74	3.39	2.55	2.55
LR -	0.62	0.51	0.54	0.43	0.39	0.39
Accuracy (%)	61.5	66.7	65	76.9	71.8	71.8
Adjusted AUC	0.719	0.798	0.805	0.867	0.86	0.895
Observed AUC (95%CI)	0.614 (0.512-0.716)	0.693 (0.595-0.79)	0.7 (0.604-0.797)	0.762 (0.656-0.869)	0.755 (0.647-0.864)	0.79 (0.647-0.

Author's conclusion: APRI alone was superior to TE alone in detecting ≥F2. APRI alone is good in detecting both F2 and ≥F3. TE was good in detecting ≥F3. The combination of TE and APRI could increase diagnostic accuracy by <5%. The combination did not add much benefit in detecting F2 or F3 and greater.

Notes: % of cirrhotic patients was small as patients with cirrhosis who already had clinical or biological signs of cirrhosis were not included. The low number of patients in the F4 category may skew data distribution and probably contribute to the low cut off points of TE.

As a result of the small sample size, ROC analyses were not performed for F4.

Author, year	Study type	Number of patients/ no. excluded from analysis and reasons (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes Loss to follow up	Source of funding
Vigano 2011A	2 cohorts Cross-sectional	254 consecutive patients Training: 128 Validation: 96 _____ 4 patients (2%) needed a second passage to compensated for the 1st specimen which was not adequate (<2cm in length). 7 (3%) were overweight	Recruitment/setting/Country: patients referred for liver biopsy to the Liver centre, Italy Inclusion: treatment naïve with CHB, with persistently or intermittently abnormal ALT and serum HBV DNA (>3 log10 UI/mL for >6 months. Exclusion: Patients with HCV, HDV and HIV co-infections, other concomitant liver diseases, current or previous liver decompensation, current or previous antiviral treatment and/or an absolute contraindication to LB (platelets <60 x 109/l, INR >1.35) Baseline characteristics Male, n (%): 154 (71) Age (years) *: 47 (18-68) Biochemical parameters* ALT (IU/L): 69 (11-855) AST (IU/L): 46 (16-559) Albumin (g/L): 4.3 (3.6-5.2)	Transient elastography (Fibroscan) Assessment performed by 3 experienced hepatologists who were blinded to clinical, biochemical and histological data. 10 successful acquisitions were performed on each patient. Success rate was calculated. Median value was taken.	Liver biopsy All patients underwent ultrasonic guided LB, carried out by 2 experienced hepatologists. Liver specimens were considered as adequate size if longer than 2cm. Liver specimens results were read by a liver pathologist blind to TE and clinical data.	METAVIR Significant fibrosis: F2-4 Cirrhosis: F4	AUC and its 95% CI (Mann-Whitney) Sensitivity Specificity PPV, NPV Confirmatory thresholds were identified with specificity >90% and LR+ ≥10; exclusion threshold, with sensitivity >90% and LR- ≤0.1 to rule in or rule out sig. fibrosis	Not stated

		(BMI >25kg/m2), 7 had unreliable TE results (3 in training set, 4 in validation set) Final N=217	Platelet x 109/L: 185 (97-304) Total bilirubin (µM/L): 0.7 (0.1-2.8) HBV DNA, log10 copies/mL*: 6.3 (1.3-9) Alcohol (%) >60g/d for men, >40g/day for women: 13 (6) HBeAg (-) (%): 169 (78) BMI >25 (%): 63 (29) METAVIR stage (%) 0,1: 89 (41) 2,3: 84 (39) 4: 44 (20) TE values, kPa*: 8.1 (3.4-62)		Each sample included >12 portal tracts (range 24-44)		and cirrhosis.	

Results

The diagnosis of significant fibrosis by TE

Overall accuracy for fibrosis: 85% (95% CI=77-91%)

Single cut off 8.7kPa

	Sig. fibrosis	No sig. fibrosis
>8.7kPa	96/125 (77%) (TP)	5/59 (8%) (FP)
<8.7kPa	(FN)	(TN)

Overall accuracy for cirrhosis: 94% (95% CI=90-98%)

Overall cohort (N=217)

	Significant fibrosis	Cirrhosis
Cut off	Sen: ≤6.2 Spec:>9.4	Sen:≤9.4 Spec:>13.1
Sensitivity to exclude (%)	94	98
Specificity to confirm (%)	96	95
LR+	14	14
LR-	0.1	0.02
Overall accuracy to exclude and confirm	91	94

Additional results: results according to different ALT levels

Author's conclusion: A dual cut off algorithm allowed for correctly classified both significant fibrosis, and cirrhosis in the majority of the patients with CHB, independent of ALT levels, thus reducing the need for liver biopsy investigation.

Notes:

Author, year	Study type	Number of patients / no. exclude	Patient characteristics	Index test 1 - how is it measured?	Other index tests - how is it	Reference standard - how is it	Target condition (s)	Outcomes	Source of funding

		from analysis (if applicable)		-index test time -threshold?	measured? - index test time -threshold?	measured? - ref standard time -threshold?	Stage of fibrosis and/or cirrhosis		
Poynard 2009	Retrospective (from a RCT)	695 _____ Final N = 462 233 excluded: 142 Serum/ biopsy not available; 30 duration between serum and biopsy was >180days; 62 a high risk profile of FP/FN	Recruitment/setting/Country: enrolled into RCT, Greece Inclusion: Patients with CHB (HeAg + and -) randomised in 2 trials of ADV vs. placebo, with available paired liver biopsies and adequate fibrotest-actitest at baseline and after 48 weeks of treatment. Time interval between serum and biopsy was <180days. Exclusion: Baseline characteristics HBeAg+ N=349 / HBeAg- N=184 Male (%): 71 / 87 Age (years), mean (SD): 36(11.2) / 46 (9.8) Race (%) White: 36 / 71 Asian: 59 / 24 Black: 3 / 5 Other: 2 / 0 HBVDNA x 106 (SD): 8.2 (0.9) / 7.1 (0.8) Knodell necroinflammatory: 7.7 (2.8) / 7.8 (2.6)	Fibrotest Blindly assessed according to recommender procedures.	Actitest Serum markers in Fibrotest + ALT	Liver biopsy Knodell/ Ishak scoring system converted to METAVIR scoring system LB specimens evaluated by independent histopathologist who was blinded to patients; treatment assignments or the timing of LB Ishak F0F1= METAVIR F0	METAVIR Significant fibrosis: F2-4 Advanced necro-inflammatory activity: A2-3	AUC* and its 95% CI *AUC was expressed with standardisation according to the prevalence of fibrosis stages defining advanced and nonadvanced fibrosis to prevent spectrum bias Sensitivity Specificity PPV NPV	Research grants from ARECA, Association pour la Recherche sur les Maladies Hepatiques Virales

		(FT-AT) was suspected at the 1st of 2nd sample.	score Knodell fibrosis score	 1.8 (1.1)	 1.9 (1.2)			IshakF2= METAVIR F1 Ishak F3=METAVIR F2 Ishak F4= METAVIR F3 Ishak F5F6= METAVIR F4			

Results

Both at baseline and after treatment

Fibrotest	Advanced fibrosis		Cirrhosis
	Observed AUC (95% CI)	Adjusted AUC (95% CI)	Adjusted AUC (95%CI)
Overall	0.76 (0.73-0.80)	0.81 (0.79-0.83)	0.82 (0.77-0.86)
Sensitivity analyses			
HBeAg (+) HBeAg (-)	0.78 0.74	0.82 0.77	--
Duration between serum and LB ≥60days <60days	 0.51 0.77	 0.56 0.81	--
Sample Baseline After treatment (48 weeks)	 0.75 0.77	 0.79 0.81	--

	Advanced necroinflammatory activity
Actitest	0.81 (0.78-0.83)

Impact of ADV on fibrosis estimated using biopsy or Fibrotest:

Fibrotest and biopsy found similar results for most of the comparisons, e.g. fibrosis decrease was greater in patients with advanced fibrosis at baseline and in patients with virological response.

Predictive values of fibrotest-actitest assuming liver biopsy had no failure:

If Fibrotest was used for treating patients with ≥F2 at baseline

Cut off	0.48	n
Sensitivity	66%	112/170
Specificity	69%	202/292
Positive predictive value	55%	112/202
Negative predictive value	78%	202/260

2x2 table (calculated from results reported by the paper)

Test	≥F2 (fibrosis)	<F2 (no fibrosis)	total
>0.48	112 (TP)	58 (FP)	170
<0.48	90 (FN)	202 (TN)	292
Total	202	260	462

If Actitest was used for treating patients with A2 at baseline:

Cut off	0.52	n
Sensitivity	70%	261/374
Specificity	60%	53/88
Positive predictive value	88%	261/296

Negative predictive value	32%	53/166

2x2 table (calculated from results reported by the paper)

Test	≥F2 (fibrosis)	<F2 (no fibrosis)	total
>0.52	261 (TP)	113 (FP)	374
<0.52	35 (FN)	53 (TN)	88
Total	296	166	462

Additional results: sensitivity analyses according to race, gender, age and biopsy length.
Analysis of discordant cases assuming that biopsy could have failures (not extracted).

Author's conclusion: Fibrotest-Actitest provides a quantitative estimate of liver fibrosis and necroinflammatory activity in patients with CHB and may be alternative to reduce the need for liver biopsy.

Notes:

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Other index tests - how is it measured? - index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Sokucu 2010	Cross-sectional	25 consecutive	Recruitment/setting/Country: Istanbul Medical School, Turkey	Fibrotest	Actitest	Liver biopsy	Ishak score	AUC and its 95% CI	Schering-Plough Corporat

			Inclusion: Children with CHB underwent percutaneous liver biopsy; the infection had been vertically transmitted in all; all patients had circulating HBV DNA and compensated chronic HBV infection. Exclusion: Any other cause of chronic liver disease, co-infection with HCV or HIV, and co-morbidities that could confound the results of the non-invasive markers (e.g. haemolysis, Gilbert's syndrome, haematological causes of thrombocytopenia. Baseline characteristics	Numerical quantitative estimate 0.00-1.00 Indices corrected for age and gender Cut off: <0.31 in Fibrotest correspond to insignificant fibrosis	Serum markers in Fibrotest + ALT Numerical quantitative estimate 0.00-1.00 Cut off values: <0.37 correspond to insignificant activity (from Poynard 2004)	Obtained with an 18-G Menghini-type needle Analysed by a single-blinded pathologist All samples were adequate and included >5 portal areas, regardless of their size.	Significant fibrosis: F3-F6 Insignificant fibrosis: F0-F2 Significant necroinflammatory activity: A0-1 Insignificant necroinflammatory activity: A2-4	Sensitivity Specificity PPV, NPV	ion, Turkey

Male, n (%)	19(76)
Age (years), median (min-max)	9 (3-18)
ALT (IU/L), mean (min-max)	134.7 (63-292)
Fibrotest score*	0.11 (0.02-0.58)
ActiTest score*	0.48 (0.06-0.79)
Fibrosis stage(%) Insig (F0-2) Sig (F3-6)	 16 (64) 9 (36)
Activity stage (%) Insig (A0-1) Sig (A2-4)	 21 (84) 4 (16)
ActiTest stage (cut off 0.37) (%) Insig Sig	 6 (24) 19 (76)

			FibroTest stage(cut off 0.31)(%) Insig Sig	 23 (92) 2 (8)					
			*median (min-max)						

Results

Fibrotest

Test	≥F3-6 (sig. fibrosis)	<F0-2 (insig. fibrosis)	total
>0.31	0 (TP)	9 (FP)	9
<0.31	2 (FN)	14 (TN)	16
Total	2	23	25

PPV=0%

NPV=61%

ActiTest

Test	≥A2-4 (sig. activity)	<A0-1 (insig. activity)	total
>0.36	4 (TP)	0 (FP)	4
<0.36	15 (FN)	6 (TN)	21
Total	19	6	25

PPV=21%

NPV=100%

Author's conclusion: Fibrotest and ActiTest does not appear ready for use in detecting either the stage of fibrosis or activity in children with CHB. Due to the small number of patients in the study, study findings need to be confirmed by further studies with larger sample sizes.

Notes:

Author, year	Study type	Number of patients/ no. excluded from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Other index tests - how is it measured? - index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Chen 2012	Cross-sectional	389 Training set: 155 Validating set: 155 _____ Final N = 315 61 excluded due to inadequate LB sample size (<1.5cm) and/or <10 portal tracts,	Recruitment/setting/Country: Nanfang hospital, China. Patients were randomly enrolled in a training set and validation set. Inclusion: treatment naïve patients with CHB. All patients were given percutaneous liver biopsies and routine lab tests. Exclusion: autoimmune liver disease, alcoholic fatty liver disease or non alcoholic steatohepatitis, co-infection with other hep viruses and other hepatobiliary diseases. BMI >26 were also excluded to ensure successful TE. Baseline characteristics Male, n (%): 254 (80.6) Age (years)*: 31.2±8.9 Biochemical parameters* ALT (U/L): 93 (8-1390)	Transient elastography (Fibroscan) Performed by 3 trained operators trained within one week of liver biopsy At least 10 successful measurements (success rate of >60% and IQR/ median ratio <30% were considered	APRI Routine lab tests were performed within 3 days of TE, including, ALT, AST, albumin, bilirubin and prothrombin time	Liver biopsy Only specimens of ≥1.5cm length containing ≥10 portal tracts were included. All biopsies were read by a single liver pathologist without knowledge of liver stiffness.	METAVIR score Cirrhosis: F4 vs. F0-3	AUC and its 95% CI (Mann-Whitney) Sensitivity Specificity PPV, NPV Likelihood ratio Optimal cut off values for TE were chosen to obtain LR+ >10 for confirming diagnosis and LR- <0.1 for	Not stated

		except for METAVIR F4 (n=56) or unreliable liver stiffness (n=5). 13 decompensated patients with CPS ≥7	Albumin (g/L) 41.95 (29.8-64.9) Platelet x 109/l 181 (38-492) Prothrombin time (s) 12.7 (10-18.3) Total bilirubin (mg/L) 0.78 (0.22-2.74) HBeAg (+) (%) 191 (60.6) Liver stiffness (kPa)* 12.2±7.8 Fibrosis stage (%) F0 7 (2.2) F1 65 (20.6) F2 99 (31.4) F3 70 (22.2) F4 74 (23.5) *mean±SD **median (range)	reliable). Median values were taken.				excluding diagnosis.	

Results

AUC (95% CI)	F4 cirrhosis vs. F0-3
TE	0.88 (0.84-0.92)
APRI	0.68 (0.61-0.75

Liver stiffness cutoffs for discriminating liver cirrhosis in CHB patients

	Excluding cirrhosis	Confirming cirrhosis
Cut off	10.4	22.3
Accuracy	0.759	0.819
Sensitivity	0.932	0.297
NPV	0.977	0.822
LR-	0.09	0.72

Specificity	0.705	0.971
PPV	0.493	0.793
LR+	3.0	10.2

Additional results: AUC for liver stiffness-spleen diameter to platelet ratio index (not extracted). Predictive value of TE according to ALT levels and bilirubin.

Author's conclusion: Transient elastography is a reliable non-invasive method for cirrhosis in patients with compensated CHB.

Notes:

Author, year	Study type	Number of patients/ no. excluded from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Wai 2006	Retrospective	377 Consecutive patients 141 in the training set 77 in the	Recruitment/setting/Country: University hospital, Singapore Inclusion: treatment naïve CHB patients who underwent percutaneous liver biopsy Exclusion: other causes of liver disease such as CHC, coinfection with HDV, hepatocellular carcinoma, prior liver transplantation, prior therapy with either IFN or	APRI Lab results performed within 4 months before the liver biopsy were used for the	Liver biopsy Reviewed by one pathologist, blinded to the clinical characteristic of the patients	Ishak score Significant fibrosis: ≥3 Cirrhosis: 5-6	AUC and its 95% CI	Not stated

validation set

_____

Final N = 218

159 excluded because of prior or concurrent antiviral treatment.

NUC, immunosuppressive therapy, coinfection with HIV, insufficient liver tissue for staging of fibrosis, or significant alcohol intake of ≥40g/week

The population were randomly divided into 2 cohorts: 65% in the training set and 35% in the validation set.

Baseline characteristics

	Training set (n=141)	Validation set (n=77)
Male, n (%)	113 (80)	67 (87)
Age (years), mean ±SD	35±1, 34(18-70)	34±1, 33(16-70)
ALT (xULN) AST (xULN) Albumin (g/L) Platelet x 109/l Prothrombin time (s) Total bilirubin (μM)	2.81 ±0.22 1.98±0.14 40.2±0.4 205±5 13.1±0.1 13.5±0.5	3.43±0.41 2.44±0.34 40.8±0.4 210±6 12.1±0.1 13.9±0.8
Chinese by ethnicity (%)	121 (86)	66 (86)
HBeAg positive (%)	105 (76)	66 (86)
Length of LB (cm) No. of portal tract on biopsy	1.62±0.07, 1.50 (03-4.5)	1.56±0.09, 1.50 (0.4-3.7)
Ishak fibrosis score Sig fibrosis (%) Cirrhosis (%)	2.34±0.213, 2(0-6) 68(48) 26 (18)	2.22±0.22 2 (0-6) 35 (46) 15 (20)
Time of blood tests	18±1, 16(0-	23±2, 19 (1-

study. If more than 1 set of lab results were available, the results closest to the time of biopsy were used.

No LB speciment was deemed insufficient

			before LB, days (mean±SEM, median)	90)	68)					

Results

Overall (N=218)

APRI	AUC (95%CI)
Significant fibrosis	0.63 (0.55-0.71)
Cirrhosis	0.64 (0.54-0.71)

Additional results: AUC for platelet count alone, AST alone, ALT/AST ratio (not extracted)

Author's conclusion: Models with non-invasive markers in predicting histology from CHC patients were unsuitable for CHB patients. No variables consisting of simple and readily available markers were able to predict cirrhosis accurately in patients with CHB.

Notes:

Author, year	Study type	Number of patients/ no. excluded from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Gaia 2011A	Cross-sectional	70 consecutive patients	Recruitment/setting/Country: Italy Inclusion: Patients with viral or metabolic	Liver stiffness measurement by Transient elastography using	Liver biopsy All	METAVIR score	AUC and its 95% CI	Not stated

		(32% of the total population) _____ Exclusion data for the overall cohort only: 21/290 (8%) unsuccessfulLSM (<10 successful measurements or success rate <60%) due to obesity/thickness of thoracic wall; 10 LB specimens <20mm; 3 diagnosis uncertain.	chronic liver disease who underwent liver biopsy at the Hepatology Unit were enrolled. Treatment naïve. Exclusion: Patients with alcoholic liver disease (alcohol intake >40g/day) and patients with acute viral hepatitis. Baseline characteristics Male/female: 50/20 Age (years), median (range): 44 (18-61) median (range) ALT (IU/L): 70 (13-464) AST (IU/L): 46 (16-237) Platelet x 109/l: 196 (52-232) GGT (UI/L): 55 (34-99) BMI (kg/m2), median (range): 24.3 (16.7-33.1) Fibrosis (%) 0: 1 (1.4) 1: 32 (45.7) 2: 11 (15.7) 3: 4 (5.7) 4: 22 (31.4) Steatosis (%) S0: 38 (54.2) S1: 31 (44.3) S2: 2 (2.8) S3: 0	Fibroscan Performed within 6 months of liver biopsy and before any therapeutic approach, including diet and antiviral therapy. Performed by trained operators, blind to liver histology but had access to medical records of the patients. Inadequate TE measurements were automatically rejected by the software. Success rate was calculated. Median value of at least 10 successful measurements was taken. ≤5kPa: absence of fibrosis (F0) 5.1-9kPa: mild fibrosis (F1) 9.1-11kPa: moderate	speciments were analysed by an expert pathologist blinded to the results of LSM but not to the clinical and biochemical data. Patients with liver specimens <20mm in length were excluded.	Mild Fibrosis: F1 Moderate fibrosis: F2 Severe fibrosis: F3 Cirrhosis: F4	Sensitivity Specificity PPV, NPV Optimal cut off values for liver stiffness were chosen to maximise sensitivity, specificity, and diagnostic accuracy (% patients diagnosed correctly)	

				fibrosis (F2) 11.1-14.5kPa: severe fibrosis (F3) ≥14.5: cirrhosis (F4)				

Results

Median LSM values: 7.6 (3.7-30.7) kPa

	F1-4 vs. F0*	F2-4 vs. F 0-1	Severe fibrosis (F3-4 vs. F0-2)	Cirrhosis (F4 vs.F0-3)
Cut off (kPa)	--	7.2	8.9	10.6
Sensitivity (%)	--	61	64	48
Specificity (%)	--	72	84	87
PPA (%)	--	71	70	63
NPA (%)	--	62	80	79
Diagnostic accuracy (%)	--	60	76	75
AUC (95% CI); SE (p value)	0.59 (0.471-0.708); 0.06 (p=0.76)	0.674 (0.544-0.805; 0.066 (p=0.014)	0.83 (0.728-0.931); 0.052 (p=<0.001)	0.763 (0.643-0.883); 0.061 (p=0.001)

*F0, n=1 patient only (median LSM=7.1kPa)

Misdiagnosis of the fibrotic stage when assessed by TE in CHB patients

	F0	F1	F2	F3	F4
n patients	1	32	11	4	22
Correct diagnosis (%)	0	53	9	25	45
Underestimation (%)	0	0	73	0	54
Overestimation (%)	100	47	18	75	0

Additional results: --

Author's conclusion: This study confirms that TE can be considered a valid support to detect fibrosis in chronic liver disease related to HCV but it should be interpreted cautiously in CHB patients, where host or disease-related factors may modify its accuracy.

Notes: quality – steatosis; severe fat infiltration was diagnosed in 3% CHB; no info on co-infection, HBeAg status; time interval

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Yilmaz 2011	Retrospective	207	Recruitment/setting/Country: Tietiary health care setting in Turkey Inclusion: patients underwent liver biopsy Exclusion: other forms of viral hepatitis and HIV. Other conditions known to cause liver dysfunction Baseline characteristics M/F: 70/137 Age (years), mean ±SD: 43.4 ±12.2 Median (IQR)* AST (U/L): 37 (25)	APRI (serum markers data from routine test) Unclear about time interval between serum collection (calculation) and LB.	Liver biopsy Specimens were reviewed by one pathologist who was blinded to patients details and clinical data	METAVIR score Fibrosis vs. no fibrosis (F1-4 vs. F0)	AUC and its 95% CI Sensitivity Specificity	Not stated

Platelet (no/mm3)	224714±62542
GGT (U/L)	42 (42)
Mean BMI (kg/m2) ± SD	26.9±3.8
Fibrosis score Median (IQR)* Mean ±SEM	 1(2) 1.14±0.09
APRI Median (IQR)*	 0.46 (0.38)

*difference between 75th percentile and 25th percentile

Results

	F1-4 vs. F0
Optimal cut off	>0.36
Sensitivity (%)	55
Specificity (%)	75.4
AUC (95% CI); SE (p value)	0.541 (0.457-0.622);0.047 (p=0.622)

Additional results:

Author's conclusion: The APRI shows an acceptable accuracy for the assessment of liver fibrosis in patients with CHC and NAFLD, but not in those with CHB.

Notes: paper also reported results on other populations – HCV and NAFLD.

Author, year	Study type	Number of patients / no. exclude from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Shin 2008	Retrospective	264 consecutive patients 173 in the estimation set 91 in the validation set _____ 73 excluded: Biopsy specimens had < 6 portal	Recruitment/setting/Country: Korea Inclusion: CHB patients with percutaneous liver biopsy Exclusion: additional causes of chronic liver diseases such as HCV or coinfection with HDV, clinically overt cirrhosis on the biasis of ultrasonography and or esophasgogastroduodenoscopy, antiviral treatments before liver biopsy, alcohol intake >20g/day in men and >10g/day in women, HIV infection. Baseline characteristics Male, n (%): 230 (87.1) Age (years), mean ±SD: 27.6 ±9.1 ALT (IU/L) mean± SD: 237.1 ± 298.7 median (range): 144.5 (9-3186) AST (IU/L)	APRI Time interval between test and ref standard – not given	Liver biopsy Reviewed by a single blinded pathologist	METAVIR and Ishak score Significant fibrosis: F2-4 vs. F0-1	AUC and its 95% CI * Sensitivity Specificity PPV, NPV Likelihood ratio *AUC of 0.85-0.95 regarded as a useful indirect marker of sig. fibrosis in this study	Not stated

		fields	mean± SD median (range) Platelet x 109/l mean± SD median (range) Length of biopsy core (mean ±SD), mm METAVIR stage (%) 0 1 2 3 4 No significant differences of the baseline data between the estimation and validation group.	138.3±150.9 95.5 (15-1586) 192.9±54.5 188(76-387) 16.9 ±3.4 15 (5.7) 108 (40.9) 63 (23.9) 69 (26.1) 9 (3.4)				

Results

Diagnostic value of APRI in predicting significant fibrosis (F≥2 vs. F0-1)

	All patients	Estimation set	Validation set
AUC (95% CI)	0.86 (0.82-0.91)	0.87 (0.82-0.92)	0.85 (0.77-0.93)
P value*	<0.0001	<0.0001	<0.0001

*P<0.05 vs. AUC 0.5

Diagnostic value of APRI in predicting significant fibrosis (F≥2 vs. F0-1) - overall sample (estimation + validation sets)

Cut off value	0.5 (n=218)	1 (n=164)	1.4 (n=132)	1.5 (n=126)	2 (n=97)
Sensitivity (%)	97	87	79	75	59

Specificity (%)	34	66	83	83	89
PPV (%)	63	74	84	83	86
NPV (%)	91	81	77	74	65

Additional results: 33% patients (86/264) had APRI between 0.5-1.4 (indeterminate category). None of the patients who had APRI <0.5 was classified as having cirrhosis (APRI ranged 1.94-14.7 in F4), and none showed APRI ≥1.4 in patients with F0 (APRI ranged from 0.19-1.07 in F0).

Author's conclusion: Of simple markers already developed in CHC, APRI may be the most accurate and simple marker for predicting significant fibrosis in CHB.

Notes: Other index tests: API, AAR, 1/platelet count

Author, year	Study type	Number of patients/ no. excluded from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Chan 2009	Cross-sectional	186 _____ Final N=161	Recruitment/setting/Country: Hospital in Hong Kong, China Inclusion: CHB patients who underwent liver biopsy between July 2006 and March 2008. No treatment was given during the 4 week period between liver biopsy exam and the LSM.	Liver stiffness measurement (LSM) using transient elastography (Fibroscan)	Liver biopsy Liver histology was assessed by two pathologists specialised in	METAVIR score No fibrosis: F0	AUC and its 95% CI Sensitivity Specificity	Not stated

		22 inadequate liver biopsy sample size; 1 unsuccessful LSM and 2 patients excluded for both reasons	Exclusion: patients who regularly consumed ≥20g/day alcohol weekly or had decompensated liver disease, complications of liver cirrhosis, previous liver surgery or liver transplantation. Baseline characteristics (N=161) Male, n (%): 122 (76) Age (years), mean ±SD: 45±11 Biochemical parameters, mean±SD ALT (IU/L): 93±78 Alkaline phosphatase (IU/L): 80±39 Albumin (g/L): 43±5 Total bilirubin (µmol/L): 15±3 Mean BMI (kg/m2) ± SD: 24 ±4.0 HBeAg (%) +: 69 (43) -: 92 (57) Log10 [HBV DNA] (copies/mL): 6.5±1.7	Performed within 4 weeks from the liver biopsy exam. 3 trained operators who had performed at least 50 measurements prior to the study were responsible for carrying out the LSM. Ten successful measurements were performed on each patient. Success rate was calculated. Median value was taken. LSM considered reliable if 10 successful asquisitions were obtained and success rate was >60%.	liver diseases blinded to clinical data Sample considered adequate if it was longer than 15mm and contained ≥ 6 portal tracts.	Bridging fibrosis: ≥F3 Cirrhosis: F4	PPV, NPV Likelihood ratio Optimal cut off for LSM were chosen either to obtain at least 90% sensitivity, at least 90% specificity, a max. sum of sen and spec and a max. diagnostic accuracy (sum of true + and true – over the total no. of patients)	

Results

AUC (95%CI)

	No fibrosis F0 vs.F1-4	Bridging fibrosis F0-2 vs. F3-4	Cirrhosis F0-3 vs. F4
AUC (95%CI)	0.80 (0.68-0.92)	0.87 (0.82-0.93)	0.93 (0.89-0.97)
P value	0.002	<0.001	<0.001

Optimal cut off values for different degrees of liver fibrosis with respect to different ALT levels

	No fibrosis (F0 vs. F1-4) (95%CI)			
Cut off*	Sen: 5kPa	Sen + Spec: 6.8kPa	Spec: 9kPa	Diagnostic accuracy: 8.4
Sensitivity (%)	92(89-97)	72 (64-79)	46 (38-54)	98 (94-99)
Specificity (%)	40 (14-73)	80 (44-96)	100 (66-100)	20 (4-56)
PPV (%)	96 (91-98)	98 (93-100)	100 (93-100)	95 (90-98)
NPV (%)	25 (8-53)	16 (7-30)	11 (5-20)	40 (7-83)
LR+	1.5 (1-2.6)	3.6 (1-12.5)	Infinite	1.2 (0.9-1.7)
LR-	0.2 (0.09-0.46)	0.35 (0.26-0.47)	0.54 (0.47-0.63)	0.1 (0.02-0.67)
Diagnostic accuracy (%)	89 (86-94)	73 (65-79)	49 (41-65)	93 (90-95)

	Bridging fibrosis (F0-2 vs. F3-4) (95%CI)			
Cut off*	Sen: 6kPa	Sen + Spec: 8.4 kPa	Spec: 11.3kPa	Diagnostic accuracy: 8.4
Sensitivity (%)	96 (88-99)	84 (74-91)	55 (43-66)	84 (74-91)
Specificity (%)	37 (27-48)	76 (65-85)	95 (88-98)	76 (65-85)
PPV (%)	58 (49-67)	77 (66-85)	91 (78-97)	77 (66-85)

NPV (%)	91 (75-98)	84 (74-91)	70 (60-78)	84 (74-91)
LR+	1.5 (1.3-1.8)	3.5 (2.4-5.3)	11.5 (4.3-30.4)	3.5 (2.4-5.3)
LR-	0.11 (0.03-0.33)	0.20 (0.12-0.35)	0.47 (0.37-0.61)	0.20 (0.12-0.35)
Diagnostic accuracy (%)	65 (56-74)	80 (10-89)	76 (66-85)	80 (10-89)

	Cirrhosis (F4 vs. F0-3) (95%CI)			
Cut off*	Sen: 8.4kPa	Sen + Spec: 9kPa	Spec: 13.4kPa	Diagnostic accuracy: 13.4
Sensitivity (%)	98 (85-100)	98 (85-100)	60 (43-75)	60 (43-75)
Specificity (%)	62 (53-71)	75 (66-82)	93 (87-97)	93 (87-97)
PPV (%)	46 (35-57)	57 (44-68)	75 (56-88)	75 (56-88)
NPV (%)	99 (92-100)	98 (93-100)	88 (80-93)	88 (80-93)
LR+	2.6 (2-3.2)	1.0 (0.93-1.0)	9.1 (4.4-18.6)	9.1 (4.4-18.6)
LR-	0.04 (0.01-0.28)	0.01 (0-0.07)	0.43 (0.29-0.63)	0.43 (0.29-0.63)
Diagnostic accuracy (%)	71 (62-77)	81 (70-86)	85 (74-95)	85 (74-95)

*Sensitivity, at least 90% sensitivity; sensitivity + specificity, a max. sum of sensitivity and specificity; specificity, at least 90% specificity; DA, a maximum diagnostic accuracy.

Additional results: Diagnostic value of LSM by ALT levels (subgroup analysis) – not extracted

Author's conclusion: Transient elastography is a reasonable noninvasive tool to substitute liver biopsy among the lowest and highest risk patients for the assessment of liver fibrosis.

Notes:

Author,	Study	Number	Patient characteristics	Index test 1	Other index	Reference	Target	Outcomes	Source

year	type	of patients		- how is it measured? -index test time -threshold?	tests - how is it measured? - index test time -threshold?	standard - how is it measured? - ref standard time -threshold?	condition (s) Stage of fibrosis and/or cirrhosis		of funding
Castera 2011	Cross-sectional	329 Consecutive patients	Recruitment/setting/Country: France Inclusion: HBeAg negative CHB patients (201/329 Inactive carriers, 61%) who underwent TE, Fibrotest, and APRI the same day (June 2003-June 2009) Inactive carrier (n=201), defined as persistently normal ALT and AST and HBV DNA <105 copies/mL (<20000IU/mL) on at least 2 determinations during the past 6 months Exclusion: Patients with other viral infection (11 HIV, 7 HCV, 5 HDV) and other causes of liver disease (17), unsuccessful LSM (43) Baseline characteristics (n=329) Male, (%): 62% Age (years), mean ±SD: 39 ±14 Biochemical parameters, ALT (IU/L) (n<50): 46±70	Transient elastography (fibroscan) Ten successful measurements performed on each patient Success rate was calculated (number validated measurements ÷ total number of measurements). Median value was taken.	Fibrotest APRI The parameters allowing calculation of fibrotest and APRI were determined in the same lab on blood samples at the time of TE. Cut offs used for diagnosing significant fibrosis and cirrhosis were those from	Liver biopsy Performed by senior operators. All biopsy specimens were analysed by the same trained pathologist blinded to the results of non-invasive tests.	METAVIR score Significant fibrosis: F2-4 Cirrhosis: F4 Necro-inflammatory activity A0 none A1 mild A2 moderate A3 severe	AUC and its 95% CI Sensitivity Specificity PPV, NPV Likelihood ratio	Not stated

			AST (IU/L) (n<50) Platelet x 109/l	37±41 227±72	Unsuccessful results, defined as either failure (no valid measurement) or unreliable results (<10 valid measurements or <60% success rate or IQR >30% median) Cut-offs used for diagnosing significant fibrosis (>7.2kPa) and cirrhosis (>11.0kPa) were those proposed by Marcellin et al.	original publications : Fibrotest Sig. fibrosis >0.48 Cirrhosis >0.74 APRI Sig. fibrosis >0.5 Or ≥1.5 and <1 or ≥2				
			Mean BMI (kg/m2) ± SD	24.5 ±4.0						
			HBV DNA (IU/mL)	2.7±17.1x 106						
			Inactive carriers							
			Male, (%)	54%						
			Age (years), mean ±SD	36 ±12						
			Biochemical parameters, ALT (IU/L) (n<50) AST (IU/L) (n<50) Platelet x 109/l	 75±106 27±8 237±67						
			Mean BMI (kg/m2) ± SD	23.7±3.8						
			HBV DNA (IU/mL)	1.5±2.7 103						
			HBeAg (-) patients							
			Male, (%)	76%						
			Age (years), mean ±SD	44 ±16						
			Biochemical parameters, ALT (IU/L) (n<50) AST (IU/L) (n<50) Platelet x 109/l	 75±106 55±61 213±79						
			Mean BMI (kg/m2) ±	24.4±4.1						

SD	
HBV DNA (IU/mL)	7.4±27.9x 106

Results

Diagnostic performance of TE, Fibrotest and APRI in the 60 patients with a liver biopsy

Transient elastography	Sig. fibrosis F≥2	Cirrhosis (F4)	Cirrhosis (F4)
Cut offs	>7.1kPa	>9.6kPa	>11kPa
Sensitivity (%)	68	87	73
Specificity (%)	63	80	87
PPV (%)	83	59	65
NPV (%)	42	95	91
LR+	1.84	4.35	5.31
LR-	0.51	0.16	0.31
AUC (95%CI)	0.76 (0.63-0.90)	0.89(0.80-0.98)	0.89(0.80-0.98)
Correctly classified (%)	67	82	83

Fibrotest	Sig. fibrosis F≥2	Cirrhosis (F4)
Cut offs	>0.48	>0.74
Sensitivity (%)	61	47
Specificity (%)	81	91
PPV (%)	90	67
NPV (%)	43	84
LR+	3.21	5.20
LR-	0.48	0.58
AUC(95%CI)	0.71 (0.58-0.85)	0.74 (0.58-0.90)
Correctly classified (%)	67	80

APRI	Sig. fibrosis F≥2		Cirrhosis (F4)	
Cut offs	<0.5	≥1.5	<1.0	≥2.0
Sensitivity (%)	62	14	47	13
Specificity (%)	64	100	80	96
PPV (%)	38	100	44	50
NPV (%)	64	30	82	76
LR+	1.72	Infinite	2.35	3.25
LR-	0.59	0.86	0.66	0.9
AUC(95%CI)	0.66 (0.50-0.82)	--	0.79 (0.67-0.91)	--
Correctly classified (%)	--	27	--	63

Additional results:

Author's conclusion:

Notes:

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Other index tests - how is it measured? - index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding

<table>
<tr>
<td>Wong 2010</td>
<td>Cross-sectional</td>
<td>156

(82 newly recruited CHB patients who had liver biopsy performed formed the validation set.</td>
<td>Recruitment/setting/Country: Hong Kong China (training group – same pop as Chan 2009)

Inclusion: Treatment naïve

Exclusion: ALT>1-5 times ULN, coinfection with HCV, other liver diseases, decompensated liver cirrhosis or hepatocellular carcinoma.

Baseline characteristics
<table>
<tr><th></th><th>Training</th><th>Validation</th></tr>
<tr><td>N</td><td>156</td><td>82</td></tr>
<tr><td>Male, n (%)</td><td>119 (76)</td><td>71 (87)</td></tr>
<tr><td>Age (years), mean ±SD</td><td>45 ±11</td><td>42±12</td></tr>
<tr><td>ALT (IU/L) (%)*
Normal
>1-5xULN</td><td>
58 (37)
98 (63)</td><td>
5 (6)
77 (94)</td></tr>
<tr><td>AST (IU/L)</td><td>54±39</td><td>75±42</td></tr>
<tr><td>Albumin (g/L)*</td><td>43±5</td><td>43±3</td></tr>
<tr><td>Platelet x 109/l</td><td>210±56</td><td>209±45</td></tr>
<tr><td>Total bilirubin (µmol/L)</td><td>15±13</td><td>16±8</td></tr>
<tr><td>Gamma-globulin (g/L)*</td><td>37±6</td><td>37±4</td></tr>
<tr><td>Mean BMI (kg/m2) ± SD</td><td>24 ±3</td><td>24 ±4</td></tr>
<tr><td>No. portal tracts*</td><td>10±5</td><td>16±8</td></tr>
</table>
</td>
<td>APRI

Cut off values of the best performing serum test formula, defined as the formula with the highest AUC curve, based on >90% sen to exclude and >90% specificity to confirm advanced fibrosis in the training and validation sets.</td>
<td>Transient elastography (Fibroscan)

Performed within 1 week from the LB exam.</td>
<td>Liver biopsy

Each liver specimen was assessed independently by two histopathologists, blinded to patients' clinical data.

Adequate if >15mm and contains 6 portal tracts</td>
<td>METAVIR score

Advanced fibrosis: F3-4

Cirrhosis: F4 vs. F0-3</td>
<td>AUC and its 95% CI

Sensitivity

Specificity

PPV, NPV

Likelihood ratio</td>
<td>The Control of Infectious Diseases grant</td>
</tr>
</table>

Length of LB (mm)	19±4 / 20±4
METAVIR fibrosis score	
F0	10 (6) / 5 (6)
F1	29 (19) / 29 (35)
F2	43 (27) / 27 (33)
F3	34 (22) / 5 (6)
F4	40 (26) / 16 (20)

*P<0.05, statistically significant

Results

Diagnostic performance of different tests and liver stiffness measurement for the presence of advanced fibrosis in the training and validation cohorts (%)

APRI*	Training cohort		Validation cohort	
Cut off	Exclusion strategy	Confirmatory strategy	Exclusion strategy	Confirmatory strategy
Sensitivity	96	60	100	81
Specificity	8	62	3	25
PPV	52	62	26	27
NPV	97	60	100	79
TE (Fibroscan)				
AUC (95%CI)	0.88 (0.85-0.91) (p<0.001)		0.80 (0.68-0.92 (p<0.001)	
Cut off	Exclusion strategy ≤6kPa for normal ALT ≤7.5 for elevated ALT	Confirmatory strategy >9kPa for normal ALT >12kPa for elevated ALT	Exclusion strategy ≤6kPa for normal ALT ≤7.5 for elevated ALT	Confirmatory strategy >9kPa for normal ALT >12kPa for elevated ALT
Sensitivity	95	54	81	43

Specificity	58	99	61	87
PPV	70	98	71	53
NPV	92	67	61	82
LR +	2.3	54	2.1	3.3
LR -	0.1	0.5	0.3	0.7
No. biopsy correctly avoided (%)	44/82 (54)	43/74 (58)	37/61 (61)	9/21 (43)
No. incorrect diagnosis (%)	4/82 (5)	1/74 (1)	4/61 (7)	8/21 (38)

*exclusion strategy=>90% sensitivity

**confirmatory strategy=>90% specificity

Additional results:

Author's conclusion:

Notes:

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Wu 2010A	Retrospective	78 consecutive	Recruitment/setting/Country: Zhongshan Hospital, Fudan University, China	APRI [AST(/ULN)/PLT (109/L)]x100	Liver biopsy	METAVIR scoring system	AUC and its 95% CI (also	Grant for Master Degree

		patients	Inclusion: patients with CHB based on HBsAg and fluctuated ALT underwent liver biopsy Exclusion: chronic liver disease due to other causes or coinfection with HDV, clinically overt cirrhosis, previous or concomitant anti-HBV therapy, alcohol consumption exceeding 20g/d in men and exceeding 10g/d in women. Baseline characteristics Male, n (%): 66 (84.6) Age (years), mean ±SD: 32.6 ±12.3 CHB family history, n (5): 29 (37.2) ALT (median, IQR), U/L: 115 (55-241) Log HBV DNA (mean ±SD): 6±1.9 AST (median, IQR), U/L: 67.5 (38-121) GGT, (median, IQR), U/L: 52.5 (27-76) HBeAg positive, n (%): 55 (70.5) Liver specimen length (mean ±SD, mm): 18.2±3.4 METAVIR activity score A0: 4 (5.1)	Liver biopsy was performed and blood serum was obtained at admission. No information on blinding of results or patients clinical characteristics.	No details on LB measurement and blinding status of investigators.	Significant fibrosis: F≥2 Severe fibrosis: F≥3	adjusted for observed AUC developed by Poynard 2007,2008) Sensitivity Specificity PPV, NPV Likelihood ratio Using cut offs according to original studies (no reference given)	Students of Fudan University

			A1 A2 A3	41 (52.5) 32 (41.1) 1 (1.3)				
			METAVIR fibrosis score F0 F1 F2 F3 F4	 13 (16.7) 33 (42.3) 13 (16.7) 10 (12.8) 9 (11.5)				

Results

Diagnostic value of APRI according to different cut offs for the diagnosis of significant and severe fibrosis

	Significant fibrosis (≥2)		Severe fibrosis (≥3)	
Cut off values	<0.50	>1.50	Not reported	Not reported
Sensitivity	0.84	0.47	Not reported	Not reported
Specificity	0.35	0.80	Not reported	Not reported
PPV	0.47	0.62	Not reported	Not reported
NPV	0.76	0.69	Not reported	Not reported
LR +	1.29	2.35	Not reported	Not reported
LR -	0.46	0.66	Not reported	Not reported
AUC (95%CI)	0.71 (0.59-0.83)		0.80 (0.67-0.92)	
Adjusted AUC	0.75		--	

Percentage of classifiable subjects, correct prediction, diagnostic accuracy and biopsies that could be avoided, n (%)

APRI	Cut offs	Classifiable subjects (%)	Correct prediction (%)	Diagnostic accuracy (%)	Biopsy avoided (%)
	<0.50	21 (27)	16 (76)	67	31 (40)

	>1.50	25 (32)	15 (62)		

Additional results:

Author's conclusion:

Notes: Also included other index tests or non-invasive liver fibrosis models such as Hepascore and Fibrometer. Selective reporting (severe fibrosis)?

Author, year	Study type	Number of patients/ no. excluded from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Myers 2010B	Cross-sectional	68 _____ 9 patients excluded n=2, inadequate biopsies for histological interpretation; n=7, LSM failures (due to overweight/obese)	Recruitment/setting/Country: 4 Canadian hepatology centres (3 academic centres and 1 community based hepatology clinic) Inclusion: North American patients with chronic liver disease (HBV, HCV or non-alcoholic fatty liver disease) who had undergone or were scheduled to undergo percutaneous liver biopsy within 6 months of LSM; treatment naïve or had discontinued antiviral therapy for at least 3 months before LSM and liver biopsy. Exclusion: contraindications to LSM (e.g. pregnancy, ascites, implantable cardiac devices); active extrahepatic infections or inflammatory disorders or malignancy, significant alcohol consumption (20g/d or more	Transient elastography using Fibroscan Operators who performed LSMs had previously completed at least 50 TE examinations At least 10 valid measurements were taken. Exams that yielded no successful measurements after at least 10	Liver biopsy Local pathologists at the centres analysed the LB specimens without knowledge of the TE results. Total length of LB specimens was recorded as a measure of the quality	METAVIR scoring system Significant fibrosis: F≥2 Bridging fibrosis: F≥3 Cirrhosis: F4	AUC and its 95% CI Sensitivity Specificity PPV, NPV Likelihood ratio Optimal LSM cut off values were determined	Not stated.

			for women, 30g/d or more for men); BMI >40kg/m2; overt cirrhosis based on routine clinical and radiographic features. Baseline characteristics (overall cohort, N=251) Female, n (%): 34 (85) Age (years), median (IQR): 49 (42-55) ALT (U/L): 61 (39-92) AST (U/L): 44 (32-68) BMI (kg/m2)*, median (IQR): 26 (23-30) Race (%) Caucasian: 60 (150) Asian: 30 (76) Other/unknown: 10 (25) METAVIR fibrosis score F0: 14 (36) F1: 33 (82) F2: 33 (82) F3: 9 (23) F4: 11 (28) Biopsy length, cm**: 2.4 (1.7-2.8) Liver stiffness, kPa: 7.7 (5.3-11.6) Success rate, % IQR/median stiffness: 100 (91-100) 0.16 (0.10-0.24) * data missing in 1 patient	attempts were considered to be failures of TE. Success rate was calculated. Median liver stiffness value was taken. An SR of <60% and/or an IQR/M of >30% was considered to be unreliable. Median interval between LB and LSM was 18 days (0-183 days).	of the ref std for staging liver fibrosis.		(maximised the sum of sen and spec). results also compared with cut off established in previous studies (only for the overall group, not only HepB).	

			**data missing in 5 patients 87% biopsies were at least 1.5cm long.					

Results

	Significant fibrosis (≥F2) (n=31)	Bridging fibrosis (≥F3) (n=8)	Cirrhosis (F4) (n=3)
Cut off	≥7.7kPa	≥10.3kPa	≥11.1kPa
Sensitivity (%) (95%CI)	61 (42-78)	75 (35-97)	100 (29-100)
Specificity (%) (95%CI)	78 (62-90)	90 (79-96)	92 (83-97)
PPV (%) (95%CI)	70 (50-86)	50 (21-79)	38 (9-76)
NPV (%) (95%CI)	71 (54-84)	96 (88-100)	100 (94-100)
AUC (95%CI)	0.75 (0.63-0.87)	0.92 (0.84-0.99)	0.97 (0.92-1.00)
Accuracy (%)(%) (95%CI)	71 (58-81)	88 (78-95)	93 (84-98)

Additional results: analyses according to ALT levels (overall cohort only). Comparison between TE and APRI (overall cohort only).

Author's conclusion: The major role of TE is the exclusion of bridging fibrosis and cirrhosis. However, TE cannot replace biopsy for the diagnosis of significant fibrosis.

Notes: Subgroup analysis (population also included HCV and NAFLD); study quoted that an AUC exceeding 0.80 are considered to be clinically useful in terms of a diagnostic test (Jaeschke et al. 1994). Baseline table for overall cohort, not only hep B. Sample size underpowered. TE examinations were performed by relatively novice operators. However, performance of TE was similar between the first and latter one-half of the study (data not shown).

Author, year	Study type	Number of	Patient characteristics	Index test 1	Reference standard	Target condition	Outcomes	Source of

		patients		- how is it measured? -index test time -threshold?	- how is it measured? - ref standard time -threshold?	(s) Stage of fibrosis and/or cirrhosis		funding
McGoogan 2010	Retrospective	36	Recruitment/setting/Country: tertiary medical centre, U.S.; using inpatient/outpatient hospital databases for ICD, 9th version, and records obtained from the clinical lab for all paediatric patients with a positive result for Hep B or C Inclusion: children 0-20 years old with chronic Hep B or C presenting at a tertiary medical centre Exclusion: incomplete data or if they were recent liver transplant recipients Baseline characteristics Male, n (%): 18 (50%) Average age (range): 11.6 (1-20) HBV (%): 11/36 (31) HCV (%): 25/36 (69) Median fibrosis score: 2 (1,2) Median APRI (IQR): 0.44 (0.24-0.97)	APRI Lab data within 4 months of liver biopsy was used for the calculations Pre-specified cut offs of 0.5 and 1.5.	Liver biopsy 6 patients had a dictated pathology report that did not assign a METAVIR score, In those cases, one investigator blinded to the patients' historical data, used the elements of the report to assign a METAVIR score range. Analysis was limited to the first reported biopsy results of the patient.	METAFIR scoring system Fibrosis: F2 or 3 Cirrhosis: F4	AUC and its 95% CI Sensitivity Specificity PPV, NPV Likelihood ratio	Not stated

			Vast majority of the patients were treatment naïve at the time of biopsy. On average, children with vertical transmission were younger than those with transfusion transmission (8 vs. 14.9y) and had lower fibrosis scores (1.1 vs. 1.6). Median fibrosis score and median APRI in HBV and HCV were not significant.					

Results

AUC for APRI in Hep B patients

	Fibrosis (F2-3)	Cirrhosis (F4)
AUC (95%CI)	0.64 (0.28-1.00)	Not applicable

Diagnostic value of APRI for prediction of fibrosis and cirrhosis in mixed hep B and C patients

	Fibrosis		Cirrhosis	
Cut off	>0.5	>1.5	>0.5	>1.5
Sensitivity	47	18	33	0
Specificity	90	100	73	91
PPV	80	100	10	0
NPV	65	58	92	91
LR+	4.5	N/A	1.2	0
LR-	0.6	0.8	0.9	1.1

Additional results:

Author's conclusion: APRI performed better in HCV patients compared to HBV patients.

Notes: small sample size, retrospective design, analysis of patients from a single centre, indirect population. Given the duration of 16years of patient records, the study is also limited by intra-interobserver variability of pathologists examining biopsy samples. No consideration of inflammatory activity. Uncertain whether HCV and HBV patient characteristics were different (Details of baseline characteristics inadequate). Results need to be interpreted with caution.

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Zhang 2008	Retrospective	137 consecutive patients	Recruitment/setting/Country: public health clinical centre, China Inclusion: CHB patients who underwent percutaneous liver biopsy. All patients were positive for HBV DNA and had no chronic liver disease. Exclusion: antiviral treatment before liver biopsy, alcohol intake >40g/d. Baseline characteristics	APRI Serum samples in all patients within 2 weeks after liver biopsy were routinely determined. Prespecified cut offs: ≥1.5 and <1.5	Liver biopsy Obtained by either blind or ultrasound guided techniques. Length of biopsy samples was longer than 1.5cm. All biopsies were read by a pathologist who had no clinical info on the patients.	METAVIR scoring system Moderate to severe fibrosis/ cirrhosis: F2-4 No to mild fibrosis/ cirrhosis: F0-1	Sensitivity Specificity PPV, NPV Likelihood ratio	Not stated

	ALT≥2ULN	ALT <2ULN
N	78	59
Male(%)	70.5	69.5
Age (years), mean (SD)	35.2 (7)	38.7 (7.4)

METAVIR fibrosis score		
F0 +1	33 (42.3)	24 (40.7)
F2	26 (33.3)	20 (33.9)
F3	13 (16.7)	9 (15.2)
F4	6 (7.7)	6 (10.1)
Sig. fibrosis (≥F4)	45 (57.3)	35 (59.3)
APRI (SD)		
F0 +1	0.55 (0.82)	0.48 (0.33)
F2	1.44 (1.79)	1.21 (1.57)
F3	1.98 (2.34)	1.69 (1.62)
F4	2.11 (1.81)	1.97 (1.73)
Sig. fibrosis (≥F4)	1.84 (1.38)	1.62 (1.45)

Biopsy specimens with ≥4 portal fields were considered representative and scored by a pathologist unaware of the lab results.

Results

	Moderate to severe fibrosis/cirrhosis (≥F2)	No to mild fibrosis (<F2)
Cut off	≥1.5	<1.5
Sensitivity	44.7	35.3
Specificity	84.3	81.6
PPV	41.3	41.3
NPV	84.7	82.2
LR+	2.8	1.9
LR-	0.66	0.79

Additional results: APRI with different hyaluronic acid cut off points

Author's conclusion:

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Liu 2011	Retrospective	623	Recruitment/setting/Country: university hospital, China Inclusion: CHB patients with a liver biopsy and with records in the histology lab database. Exclusion: other causes of liver disease such as HCV, HFV etc; hepatocellular carcinoma, prior liver transplantation; insufficient liver tissue for staging of liver fibrosis; insufficient data on complete blood count or serum markers; patients without routine and serum markers prior to drug treatment; patients accepted antiviral therapy for >3 months.	APRI Serum markers were measured and recorded within a week of liver biopsy. If more than one set of lab results were available, the set of results closes to the time of biopsy were used.	Liver biopsy Samples at least 10mm long and 1mm wide. A single pathologist who had no clinical info of patients evaluated all biopsy results.	METAVIR scoring system Significant fibrosis: F2-F4	AUC and its 95% CI Sensitivity Specificity PPV, NPV Likelihood ratio	Grant from Liaoning Provincial Natural Science Foundation

Baseline characteristics (at the time of biopsy)

	F0-1	F2-4
N	408	215
Male/Female, n	267/141	79/136
Age (years), mean ±SD	45 ±11	42±12
ALT (U/L) AST (U/L) Platelet x 109/l	95.3±110.3 53.85±61.35 181.34±50.93	161.5±189.8 108.3±119.1 150.8±49.35
APRI	0.32±0.41	0.76±0.78
HBeAg +/-	249/135 (65%)	91/112 (45%)
Log10 HBV DNA (copies/mL)	4.97±1.41	5.84±1.95
Length of LB (mm)	19±13	20±11
METAVIR fibrosis score F0 F1 F2 F3 F4	 226 (36.3) 182 (29.2) 102 (16.4) 78 (12.5) 35 (5.6)	

Results

Diagnostic value of APRI for prediction on significant fibrosis

	Significant fibrosis (≥F2)
Cut off	0.3
Sensitivity (%)	69.3
Specificity (%)	71.7
PPV (%)	56.4
NPV (%)	81.6
AUC (95%CI)	0.764 (0.726-0.803)

Additional results: Subgroup1 – patients with known duration of HBsAg positive (≤35 vs. >35y)

Author's conclusion:

Notes: 252 with known HBsAg positivity duration

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Seto 2011	Retrospective (from a trial)	129	Recruitment/setting/Country: Hong Kong Inclusion: treatment naïve CHB patients (58.4%	APRI Lab parameters	Liver biopsy An 18G	Knodell HAI and Ishak fibrosis	AUC and its 95% CI	None

			HBeAg positive) who had undergone liver biopsy were randomly divided into training group (n=108) and validation group (n=129). HBV DNA >2000IU/mL, serum ALT <10xULN prior to recruitment. Exclusion: decompensated cirrhosis or concomitant liver disease, HCV, HDV, primary biliary cirrhosis, autoimmune hepatitis, Wilson's disease, alcohol intake >20g/d for women and >30g/d for men. Baseline characteristics Validation N: 129 Male, n (%): 87 (67.4) Age (years), median (range): 40 (18-61) ALT (U/L) (%) Normal: 15 (11.6) >1-2xULN: 55 (42.6) >2xULN: 59 (45.7) AST (U/L)*: 55 (18-304) Albumin (g/L)*: 45 (36-53) Platelet x 109/l*: 198 (93-334) bilirubin *(µmol/L): 12 (3-31) HBeAg positive: 56 (43.4) HBV DNA log IU/mL)*: 6.76 (2.7-14)	were recorded at the time of liver biopsy	sheathed cutting needle was used in 33 patients, a min. length of 17G core aspiration needle was used for the remaining patients. Minimum length of biopsy sample: 2cm A single histopathologist blinded to patients' lab data.	score Significant fibrosis (at least bridging fibrosis): Ishak ≥3	Sensitivity Specificity PPV, NPV Likelihood ratio Optimal cut off determined using value with the highest sensitivity and specificity.	

			Fibrosis score (%) F0 F1 F2 F3 F4 F5 F6 Patients with fibrosis score ≥3 *median (range)	 12 (9.3) 39 (30.2) 31 (24) 25 (19.4) 12 (9.3) 8 (6.2) 2 (1.6) 47 (36.4)				

Results

Diagnostic value of APRI for prediction of significant fibrosis (validation cohort, n=129)

	Significant fibrosis (Ishak ≥3)	
AUC (95%CI)	0.708 (0.625-0.800)	
Optimal cut off	0.5	1.5
Sensitivity	89.6	29.9
Specificity	40.6	88.1
PPV	42.1	54.8
NPV	89	72.3
LR+	1.509	2.516
LR-	0.256	0.96

Additional results: AUC of the validation cohort using APRI for significant fibrosis in patients with ALT<2xULN = 0.727 (95%CI 0.636-0.818).

Author's conclusion:

Notes: different techniques were used in some patients when undergoing LB. main study objective was to derive and validate a new model (not investigating APRI). 67.6% of patients had limited fibrosis, the study would be biasd towards having a high negative predictive value. Due to the small number of patients with histologic cirrhosis, diagnostic accuracy was not investigated in this group of patients.

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Kim 2010A	Cross-sectional	521 consecutive patients	Recruitment/setting/Country: Severance Hospital in Yonsei University, Korea between Dec 2006 and Jan 2009 Inclusion: CHB patients who underwent liver biopsy. Exclusion: other causes of chronic liver disease, e.g. liver cancer, coinfection with HCV, HDV or HIV (n=14); comorbidities associated with CHB (non-alcoholic steatohepatitis, primary sclerosing cholangitis, or primary biliary cirrhosis (n=7); alcohol intake >40g/day for more than 5 years (n=7); antiviral therapy before liver biopsy; previous liver resection surgery or liver transplantation (n=13); cardiac failure (n=1); liver biopsy unsuitable for fibrosis staging (n=1)	APRI All patients systematically underwent complete biochemical workups, ultrasonagraphy and liver biopsy within 1 day. All lab data were obtained on the same day as the ultrasonagraphic exam.	Liver biopsy Fibrosis stage was assessed according to the METAVIR scoring system by a single pathologist who was unaware of the patients' histories. Specimens that were	METAVIR F0= no fibrosis F1=portal fibrosis without septa F2= few septa F3=Numerous septa without cirrhosis	AUC and its 95% CI	Liver cirrhosis clinical research centre, in part by a grant from the Brain Korea 21 Project for medical science and a grant from Ministry

			Baseline characteristics Male:female, n: 317:204 Age (years), mean ±SD: 41.1±14.7 Mmean±SD ALT (IU/L): 69±23 AST (IU/L): 50±27 Albumin (g/dL): 4.18±0.56 Platelet x 109/l: 180±66 Total bilirubin (mg/dL): 0.8±0.5 Mean BMI (kg/m2) ± SD: 23.3±3.24 Median no. portal tracts (range): 12 (11-14) Length of LB (mm), mean±SD: 21.5±5.2 METAVIR fibrosis score (%) F0: 5 (0.96) F1: 86 (16.51) F2: 164 (31.48) F3: 63 (12.09) F4: 203 (38.96)		shorted than 15mm and considered by the pathologists to be unsuitable for fibrosis assessment were excluded.	F4=cirrhosis		of Health, Welfare and Family Affairs

Results

AUC of APRI for predicting cirrhosis

	Cirrhosis (F4)

AUC (95%CI)	0.78 (0.74-0.816)

Additional results: P2/MS and other non-invasive tests that are not included in the review protocol (not extracted).

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Kim 2010B	cross-sectional	330 consecutive patients	Recruitment/setting/Country: Severance hospital, Yonsei University, Korea; enrolled between July 2008 and Aug 2009 Inclusion: CHB patients who had undergone both liver biopsy and LSM (liver stiffness measurement) on the same day. Exclusion: other causes for chronic liver disease, including liver cancer, coninfection with HCV,HDV, HIV (n=9); comorbidities associated with CHB (non-alcoholic steatohepatitis, primary sclerosing cholangitis or primary biliary cirrhosis (n=10); alcohol intake >40g/day for >5y (n=5); antiviral therapy before LB (n=18); previous liver resection surgery or liver transplantation (n=9); unreliable LSM (n=5); cardiac failure (n=2); liver biopsy unsuitable for fibrosis staging (n=3).	Transient elastography using FibroScan Performed by one trained technician. <8 successful acquisitions or a success rate of <60% were considered reliable. All the patients systematically underwent complete biochemical assessment, LSMs	Liver biopsy All liver tissue samples were evaluated by a single hepatopathologist with 15y experience, who was blinded to patients' clinical histories and LSM values. Specimens shorted than	METAVIR F0=no fibrosis F1=portal fibrosis F2=portal fibrosis with few septa F3=numerous septa without cirrhosis F4=cirrhosis	AUC and its 95% CI	Liver cirrhosis clinical research centre, in part by a grant from the Brain Korea 21 Project for medical science and a grant from Ministry

			Baseline characteristics Male:female, n: 179:151 Age (years), mean ±SD: 43.7 13.2 LSM, kPa: 14.8±12.6 ALT (IU/L): 77±28.49 AST (IU/L): 55.18±17.26 Albumin (g/L)*: 42.3±5.9 Platelet x 109/l: 174.6±66 Total bilirubin (µmol/L): 17.34±5.44 Mean BMI (kg/m2) ± SD: 23.4 ±3.19 Necro-inflammatory grades (%) A1: 208 (63) A2: 93 (28.2) A3: 29 (8.8) METAVIR fibrosis score (%) F0: 1 (0.3) F1: 36 (10.9) F2: 90 (27.3) F3: 24 (7.3) F4: 179 (54.2)	and liver biopsy within 2 days.	15mm and considered by the pathologists to be unsuitable for fibrosis staging were excluded.			of Health, Welfare and Family Affairs
Results AUC of transient elastography for predicting cirrhosis								

	Cirrhosis (F4)
AUC (95%CI)	0.92 (0.89-0.95)

Additional results: LSM-spleen diameter to platelet ratio index (not included in the review protocol – not extracted).

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Kim 2009	Cross-sectional	130 consecutive	Recruitment/setting/Country: Severance Hospital in Yonsei University, Korea; between Jan 2006 and June 2007 Inclusion: treatment naïve CHB patients who underwent liver biopsy and LSM (liver stiffness measurement). Exclusion: evidence of decompensated liver cirrhosis, such as history of variceal bleeding, severe ascites, hepatic encephalopathy, or Child pugh class B/C at the time of LB and LSM. Other causes of chronic liver disease, including liver cancer, coinfection with HCV, HIV. Antiviral treatment before LB, alcohol intake >40g/day for >5 years, any other cause of splenomegaly.	Transient elastography using FibroScan Was measured on the same day as liver biopsy. 10 validated measurements were performed on each patient. Success rate was calculated. Median value was taken. Only procedures with 10 validated measurements and a success rate of	Liver biopsy All liver tissue samples were evaluated by an experienced hepatopathologist who was blinded to patients' clinical history. Liver specimens were of any adequate size	METAVIR F0=no fibrosis F1=portal fibrosis without septa F2=portal fibrosis with few septa F3=numerous septa without cirrhosis F4=cirrhosis	AUC and its 95% CI Sensitivity Specificity PPV, NPV Likelihood ratio	Not stated.

			Baseline characteristics Male/female, n (%) 103 (79.2)/27 (20.8) Age (years), mean ±SD 42.5±13.2 ALT (IU/L) 45.1±23.4 AST (IU/L) 37±15.4 Albumin (mg/dL) 4.3±0.5 Platelet x 109/l 169±62 Total bilirubin (mg/dL) 0.84±0.32 HBV DNA (≥105 copies/mL) (%) 65 (46.2) Liver stiffness score, IQR (ka) 13.1 ±10.7/1.9±2.0 Mean BMI (kg/m2) ± SD 25.3±1.3 HBeAg positivity (%) 76 (58.5) Stage of activity A0 54(41.5) A1 40 (30.8) A2 24 (18.5) A3 12 (9.2) METAVIR fibrosis score F0 0(0) F1 10 (7.7) F2 37 (28.5) F3 16 (12.3) F4 67 (51.5)	≥60% were considered reliable. Also combination of TE and APRI Optimal cut off values were chosen to maximise the sum of sensitivity and specificity	and quality, and ≥6 portal tracts were assessed.			

Results

AUC (95%CI)	Cirrhosis (F4)
LSM	0.84 (0.77-0.91)
LSM + APRI	0.85 (0.78-0.91)

Diagnostic value of LSM in predicting cirrhosis

	Cirrhosis (F4)
Cut off	10.1kPa
Classified cases, n (%)	51/67 (80.9)
Sensitivity (%)	76.1
Specificity (%)	81
Positive predictive value (%)	76.1
Negative predictive value (%)	80.9

Additional results: APRI results, replaced by Kim 2010A.

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time	Target condition (s) Stage of fibrosis and/or	Outcomes	Source of funding

					-threshold?	**cirrhosis**		
Cardoso 2012	Cross-sectional	202 Original N=221 19 excluded from the analysis (14 unreliable results and 5 unsuccessful tests)	Recruitment/setting/Country: France (single centre) Inclusion: treatment naïve CHB patients with compensated HBV infection, consecutively admitted between 2006 and 2008. Exclusion: excessive alcohol intake, co-infection with HIV and/or HDV, other causes of liver disease, decompensated liver disease or hepatocellular carcinoma, and previous liver surgery or liver transplantation. Baseline characteristics Male (%): 80 Age (years), mean ±SD: 41 (11) Origin (%) Caucasian: 21 Asiatic: 26 other: 53 ALT x ULN (IU/L), median (IQR): 2.1 (0.9-2.0) Albumin (g/dL): 4.4 (0.5) Platelet x 109/l: 206 (62) HBV DNA (log UI/ml, mean (SD)): 4.9 (1.90) Mean BMI (kg/m2) ± SD: 24.2 (3.4)	Transient elastography using FibroScan Was measured prior to liver biopsy on the same day of the procedure and by a single experienced operator. Measurements were performed by using the standard technique. Patients with at least 10 valid measurements (with IQR <30% of the median stiffness, and with at least 60% success rate) were included in the analysis. Pre-specified cut off values: 7.2kPa for F≥2 8.1kPa for ≥F3 11kPa for F4	Liver biopsy Performed under ultrasound guidance using the Menghini technique with disposable 16-gauge diameter needles. A single experienced pathologist who was unaware of the clinical data evaluated all samples. The length of each liver fragment and the number of portal tracts were recorded and only patients with liver	METAVIR F2-4= significant fibrosis F3-4= advanced fibrosis F4= cirrhosis	AUC and its 95% CI Sensitivity Specificity PPV, NPV Likelihood ratio	Not stated.

			Obesity (%) 7 HBeAg positivity (%) 24 Stage of activity A0 53 (26) A1 103 (51) A2 42 (21) A3 4 (2) METAVIR fibrosis score F0 28 (14) F1 89 (44) F2 51 (25) F3 18 (9) F4 16 (8) Median of TE (kPa) F0 5.1 F1 5.3 F2 7.8 F3 10.8 F4 14.5	Cut off values adjusted according to ALT levels Normal ALT: 6.0kPa for F≥2 9.0kPa for ≥F3 12.0kPa for F4 ALT 1-5xULN: 7.5kPa for F≥2 12.0kPa for ≥F3 13.4kPa for F4	biopsy length ≥15mm and/or at least 6 portal tracts were included.			

Results

Mean biopsy length 19.7 (SD 6.4) mm, with a median of 20mm (IQR=17-22mm).
The median number of portal tracts = 12 (IQR=10-20)

	F≥2	F≥3	F4
AUC (SE)	0.867 (0.026)	0.902 (0.029)	0.935 (0.024)

Diagnostic value of LSM in predicting significant fibrosis, advanced fibrosis and cirrhosis

	F≥2	F≥3	F4
Cut off	7.2 kPa	8.1kPa	11kPa
Sensitivity (%)	74	88	75
Specificity (%)	88	81	90
Postive predictive value (%)	82	48	39
Negative predictive value (%)	82	97	98
Positive likelihood ratio	6.2	4.63	7.34
Negative likelihood ratio	0.30	0.15	0.28
Overall accuracy (%)	82	82	89

Comparison of diagnostic accuracy of TE in predicting significant fibrosis according to ALT levels (different thresholds applied) (N=186)

	Normal ALT ≤1xULN	1-5xULN	Normal ALT ≤1xULN	1-5xULN
Cut off	Marcellin 7.2 kPa	7.2 kPa	Chan 6.0kPa	7.5kPa
Sensitivity (%)	61	74	78	70
Specificity (%)	92	86	69	88
Positive predictive value (%)	73	83	48	84
Negative predictive value (%)	87	78	89	76
Posiive likelihood ratio	7.49	5.34	2.54	5.78
Negative likelihood ratio	0.42	0.31	0.32	0.34
Overall accuracy (%)	84	80	72	79

Comparison of diagnostic accuracy of TE in predicting advanced fibrosis according to ALT levels (different thresholds applied) (N=186)

	Normal ALT ≤1xULN	1-5xULN	Normal ALT ≤1xULN	1-5xULN
Cut off	Marcellin 8.1kPa	8.1kPa	Chan 9.0kPa	12kPa
Sensitivity (%)	86	90	71	53
Specificity (%)	93	76	95	96

Positive predictive value (%)	60	44	63	71
Negative predictive value (%)	98	97	97	91
Positive likelihood ratio	12.86	3.74	14.29	12.11
Negative likelihood ratio	0.15	0.14	0.30	0.5
Overall accuracy (%)	93	78	93	88

Comparison of diagnostic accuracy of TE in predicting cirrhosis according to ALT levels (different thresholds applied) (N=186)

	Normal ALT ≤1xULN		1-5xULN	
Cut off	Marcellin 11kPa	11kPa	Chan 12kPa	13.4kPa
Sensitivity (%)	67	73	67	55
Specificity (%)	97	88	98	96
Positive predictive value (%)	50	40	67	60
Negative predictive value (%)	98	97	98	95
Positive likelihood ratio	21.33	6.06	42.67	13.64
Negative likelihood ratio	0.34	0.31	0.34	0.47
Overall accuracy (%)	96	87	97	92

Additional results:

Author's conclusion: TE measurement accurately predicts the absence or presence of significant fibrosis, advanced fibrosis or cirrhosis. The use of TE cut off values adjusted to ALT level did not improve performances for estimating liver fibrosis in HBV patients and needs to be validated.

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured?	Reference standard - how is it	Target condition (s)	Outcomes	Source of funding

				-index test time -threshold?	measured? - ref standard time -threshold?	Stage of fibrosis and/or cirrhosis		
Verveer 2012	Retrospective	125	Recruitment/setting/Country: outpatient clinic, the Netherlands Inclusion: CHB patients who had liver biopsy and transient elastography (TE) during the same session (from Jan 2005 to May 2008), in which the TE preceded the liver biopsy (16 patients a second biopsy and a second TE assessment were obtained at least 1 year later). Exclusion: coexistence of a second liver disease, co-infection with HIV, HCC and conditions known to cause a low success rate of TE such as ascites, obesity or narrow intercostal margins, which hamper proper placement of the TE probe. *Antiviral treatment was not an exclusion criteria. 6 patients a biopsy was performed during antiviral therapy. Baseline characteristics <table><tr><td>Male/female, n</td><td>92/33</td></tr><tr><td>Age (years), mean ±SD</td><td>36.5 (13.0)</td></tr><tr><td>Race Caucasian Asian African</td><td> 61 (48.8) 41 (32.8) 23 (18.4)</td></tr></table>	Transient elastography using FibroScan Was measured on the same day as liver biopsy. TE was considered to be reliable with 8 or more successful acquisitions and a success rate of ≥60%.	Liver biopsy Adequate liver biopsy length was at least 25mm. Two experienced hepatologists performed the liver biopsies. In some patients, two liver biopsies were required for obtaining an adequate sample size. Two hepatologists scored the specimens independently. In case of disagreement, a consensus was reached	METAVIR F0=no fibrosis F1=portal fibrosis without septa F2=portal fibrosis with few septa F3=numerous septa without cirrhosis F4=cirrhosis For the assessment of necro-inflammation the modified histology activity index (HAI) was used.	AUC The cut off values with the best discriminative ability between different fibrosis stages were determined by the maximum of the Youden index, but with the criteria of a min. of 90% sensitivity of a true high fibrosis score. The stiffness data are presented on a log scale	Not stated.

			ALT (IU/L) Platelet (g/L) Mean BMI (kg/m2) HBeAg positivity (%) Genotype A B C D E METAVIR fibrosis score F0 F1 F2 F3 F4	88.3 205 25 49/67 (40.8) 27 13 25 40 9 8 (5.7) 57 (40.7) 36 (25.7) 30 (21.4) 9 (6.4)			in a combined session.		because of the skewed distribution.	

Results

	F≥2	F≥3
AUC	0.85	0.91

*AUC for F4 (cirrhosis) was reported based on a mixed population of hep B and C patients (not extracted)

Author, year	Study type	Number of	Patient characteristics	Index test 1	Other index tests	Reference standard	Target condition	Outcomes	Source

		patients/ no. excluded from analysis (if applicable)		- how is it measured? -index test time -threshold?	- how is it measured? - index test time -threshold?	- how is it measured? - ref standard time -threshold?	(s) Stage of fibrosis and/or cirrhosis		of funding
Kim 2012B	Cross-sectional	194	Recruitment/setting/Country: Severance hospital, Korea Inclusion: Consecutive Asian CHB patients who underwent liver biopsies along with fibrotest and transient elastography on the same day (prior to treatment) between July 2008 and June 2010. Liver biopsy was performed to assess the severity of fibrosis and inflammation prior to treatment Exclusion: previous history of antiviral therapy, history of hepatocellular carcinoma treatment at the time of liver biopsy, diagnosis of malignancy other than HCC during the follow up, liver biopsy specimen shorter than 20mm, coinfection with HIV, invalid liver stiffness values with <10 successful acquisitions, success rate <60% or IQR/median value ratio >0.3, alcohol intake >40g/day for more than 5 years or ride sided heart failure. Baseline characteristics Male, n (%): 119 (61.3)	Transient elastography (Fibroscan) TE was performed by one well-trained technician on the same day as Fibrotest and liver biopsy. The TE operator was blinded to patients; clinical and laboratory data.	FibroTest All laboratory data required for calculating fibrotest score were obtained the same day as TE and liver biopsy. FibroTest score was computed on the BioPredictive website	Liver biopsy Only specimens of ≥1.5cm length containing ≥10 portal tracts were included. All biopsies were read by a single liver pathologist without knowledge of liver stiffness.	Batts and Ludwig system Significant fibrosis: ≥F2 Advanced fibrosis: ≥F3 Cirrhosis: F4	AUC and its 95% CI Sensitivity Specificity PPV, NPV	Not stated

Age (years)*	46.7 (14.7)
Biochemical parameters* ALT (U/L) Albumin (g/dL) Platelet x 109/l Prothrombin time (%) Total bilirubin (mg/dL)	 58.4 (27.1) 4.75 (1.37) 179.3 (71.2) 93.1 (13.3) 1.16 (0.9)
BMI (kg/m2)	23.4 (2.8)
HBeAg (+) (%)	Not reported
Biopsy length (mm)	21.3 (0.7)
FibroTest	0.53 (0.29)
Liver stiffness (kPa), mean (SD)	14.2 (9.5)
Fibrosis stage (%) F0 F1 F2 F3 F4	 0 (0) 30 (15.5) 50 (25.7) 39 (20.1) 75 (38.7)

Results

Diagnostic performances of liver stiffness and their suggested cut off values

	F≥2	F≥3	F4
Cut off	8.8kPa	10.2kPa	14.1kPa
AUC (95% CI)	0.873 (0.802-0.944)	0.897 (0.846-0.949)	0.91 (0.867-0.953)
Sensitivity	78	86.3	84

Specificity	86.7	90.4	84.9
PPV	97	90.4	77.8
NPV	41.9	86.3	89.4

Diagnostic performances of fibrotest and their suggested cut off values

	F≥2	F≥3	F4
Cut off	0.32	0.52	0.68
AUC (95% CI)	0.903 (0.838-0.968)	0.907 (0.862-0.952)	0.866 (0.815-0.918)
Sensitivity	79.3	86	80
Specificity	93.3	90	84
PPV	98.5	92.5	75.9
NPV	45.2	81.8	87

Diagnostic performances using combination of liver stiffness and fibrotest (LS + FT) and their suggested optimal cut off values

	F≥2	F≥3	F4
Cut off	8.2	10.7	16.8
AUC (95% CI)	0.885 (0.816-0.953)	0.905 (0.856-0.955)	0.915 (0.874-0.956)
Sensitivity	84.8	93	76
Specificity	83.3	87.5	94.1
PPV	96.5	91.4	89.1
NPV	50	89.7	86.2

Diagnostic performances using another combination formula multiplying liver stiffness by fibrotest (LS x FT) and their suggested optimal cut off values

	F≥2	F≥3	F4
Cut off	2.3	4.7	9.8
AUC (95% CI)	0.841 (0.908-0.975)	0.931 (0.889-0.974)	0.929 (0.894-0.965)
Sensitivity	82.9	92.1	80

Specificity	96.7	87.5	92.4
PPV	99.3	91.3	87
NPV	50.9	88.6	88

Additional results:

Author's conclusion: Fibrotest provides good fibrosis prediction, with comparable outcomes to liver stiffness in Asian CHB patients. Fibrotest substantially reduces need to liver biopsy, especially when used in combination with liver stiffness measurement.

Notes:

Author, year	Study type	Number of patients/ no. excluded from analysis (if applicable)	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Other index tests - how is it measured? - index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Sebastiani G et al. 2011	Retrospective	253	Recruitment/setting/Country: Europe (9 centres) Inclusion: consecutive treatment naïve patients admitted between Jan 2003 and Dec 2008. A diagnosis of well-compensated chronic liver disease of any aetiology; availability of both liver biopsy and relevant	FibroTest/Fibrosure Values were obtained through Biopredictiv	APRI Tests performed on the same day	Liver biopsy Analysed by each centre by the local pathologist who was unaware of	METAVIR Significant fibrosis: ≥F2 Advanced fibrosis: ≥F3	AUC* and its 95% CI Sensitivity Specificity PPV, NPV	Not stated

			parameters for the assessment of non-invasive biomarkers performed on the same day. Exclusion: decompensated liver cirrhosis, co morbidities that could confound the interpretation of non-invasive biomarkers, including haemolysis, Gilbert's syndrome, thrombocytopenia not liver-related, history or evidence at entry of HCC, liver transplantation. Baseline characteristics Male, n (%): 184 (72.7) Age (years)*: 43.7 (14.7) Biochemical parameters* ALT (U/L): 74.6 (50.3) Platelet x 103/mm3: 180.2 (49.2) BMI (kg/m2): 24.2 (3.5) HBeAg (+) (%): 46 (18.2) Coinfected with HDV: 13 (5.1) Fibrosis stage (%) F0: 26 (10.3) F1: 81 (32) F2: 74 (29.2) F3: 27 (10.7) F4: 45 (17.8)	e or by courtesy of Professor Poynard		clinical data.	Cirrhosis: F4	Likelihood ratio AUC was standardised / adjusted using the DANA (difference between advanced and non-advanced fibrosis) method	
Results									

Diagnostic performances of APRI

	F≥2	F4
Cut off	1.5	2.0
Accuracy	65.3	69.7
Observed AUC (95%CI)	0.64 (0.58-0.70)	0.61 (0.55-0.66)
Adjusted AUC (95% CI)	0.69 (0.63-0.76)	0.66 (0.60-0.71)
Sensitivity	36.9	20.6
Specificity	98	83.6
PPV	93.7	16.7
NPV	50	77.9
LR+	18.5	1.26
LR-	0.64	0.94

Diagnostic performances of FibroTest/Fibrosure

	F≥2	F4
Cut off	0.48	0.75
Accuracy	64	80.9
Observed AUC (95%CI)	0.69 (0.63-0.75)	0.68 (0.63-0.73)
Adjusted AUC (95% CI)	0.74 (0.68-0.80)	0.73 (0.68-0.78)
Sensitivity	54.2	42.1
Specificity	83.3	91.4
PPV	89	76
NPV	52.6	86.4
LR+	3.25	4.89
LR-	0.55	0.63

Author's conclusion:

Notes: lack of evaluation by a single pathologist (did not have a central pathologist for the interpretation of liver histology).

Author, year	Study type	Number of patients	Patient characteristics	Index test 1 - how is it measured? -index test time -threshold?	Reference standard - how is it measured? - ref standard time -threshold?	Target condition (s) Stage of fibrosis and/or cirrhosis	Outcomes	Source of funding
Raftopoulos 2012	Prospectively collected database and retrospective review of records when data incomplete	179	Recruitment/setting/Country: 4 tertiary referral centres (3 in Australia and 1 in France) Inclusion: CHB patients with detectable HBsAg and ALT <10 times upper limit of normal, without a documented recent severe flare, who had undergone a liver biopsy. Exclusion: haemochromatosis; α1-antitrypsin deficiency; Wilson disease and autoimmune or cholestatic liver disease; HIV; HCV or HDV co-infection; liver transplantation. 81 patients were excluded, 38 because sera not taken within 6 months of biopsy; 21 because of inadequate liver biopsy for staging and 5 for incomplete data. All patients were treatment naïve at the time of biopsy	APRI, FibroTest Serum markers were conducted at the time of liver biopsy.	Liver biopsy Samples at least 10mm long. Interpreted by the institutions' expert histopathologists, blinded to the results of the serum marker results.	METAVIR scoring system Significant fibrosis: F2-F4 Advanced fibrosis F3-F4 Cirrhosis F4	AUC and its 95% CI Sensitivity Specificity PPV, NPV Likelihood ratio	Grant from Seeding Research to University of W.Australia, which has licencing agreement with Quest Diagnostics regarding Hepascore. Also

			Baseline characteristics (at the time of biopsy) N 179 Male/Female, n 127/52 Age (years), mean ±SD 41.9 ±12.7 ALT (U/L) 88.6±73.3 (n=153) AST (U/L) 64.8±53.3 (n=146) Bilirubin (µmol/l) 15.4±31.0 (n=179) HBeAg +/- 24/41 (n=68) Log10 HBV DNA (copies/mL) 5.7±2.0 (n=68) Length of LB (mm) 21.0±9.7; range 10-70 Mean portal tract number 9.3 ± 4.7 METAVIR fibrosis score No (%) F0 27 (15.1) F1 77 (43.0) F2 35 (19.6) F3 25 (14.0) F4 15 (8.4) Histological activity (METAVIR) (n=178) Mean (SD) A0-1 131 (73.6) A2 30 (16.) A3 17 (9.6)				clinical research grant from Bristol Meyers Squibb, Australia Pvt Lrd

Results

Diagnostic value of APRI for prediction of significant fibrosis and cirrhosis (n=146/179)

	Significant fibrosis (≥F2)			Advanced fibrosis (F3-F4)	Cirrhosis (F4)	
Cut off	Highest Youden index >0.55	>0.5	>1.5	Not reported	Highest Youden index >0.81	>1.0
Proportion of population (%)	47	53	13	NR	29.5	22.6
Sensitivity (%)	71	79	28	NR	75	67
Specificity (%)	71	65	98	NR	75	81
PPV (%)	63	62	89	NR	21	24
NPV (%)	77	81	65	NR	97	97
LR +	2.40	2.23	11.6	NR	2.95	3.57
LR -	0.42	0.33	0.74	NR	0.34	0.41
AUC (95%CI) All patients Near-normal (<60 IU/l) ALT levels (n=71)	0.78 (95%CI 0.71 to 0.86) 0.72 (95%CI 0.56 to 0.84)			0.82 (95%CI 0.74 to 0.91) 0.77 (95%CI 0.63 to 0.92)	0.84 (95%CI 0.72 to 0.97) 0.70 (95%CI 0.44 to 0.96)	

Diagnostic value of Fibrotest for prediction of significant fibrosis and cirrhosis (n=145/179)

	Significant fibrosis (≥F2)		Advanced fibrosis (F3-F4)	Cirrhosis (F4)	
Cut off	Highest Youden index >0.37	>0.48	Not reported	Highest Youden index >0.63	>0.73
Proportion of population (%)	48	33	NR	22.1	15.2
Sensitivity (%)	67	54	NR	78	78
Specificity (%)	66	82	NR	82	89
PPV (%)	56	66	NR	22	32
NPV (%)	75	74	NR	98	98
LR +	1.96	3.00	NR	4.23	7.07
LR -	0.51	0.56	NR	0.27	0.25
AUC (95%CI) All patients Near-normal (<60 IU/l) ALT levels (n=71)	0.72 (95%CI 0.65 to 0.82) 0.62 (95%CI 0.44 to 0.79)		0.78 (95%CI 0.68 to 0.87) 0.70 (95%CI 0.50 to 0.90)	0.92 (95%CI 0.85 to 0.99) 0.93 (95%CI 0.85 to 0.1.0)	

Additional results: Subgroup1 – patients with known duration of HBsAg positive (≤35 vs. >35y)

Author's conclusion:

Notes: 252 with known HBsAg positivity duration

E.5 Genotype testing

E.5.1 Patients receiving peg interferon

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Lau et al, 2005; Peginterferon α-2a, lamivudine and the combination for HBeAg positive chronic hepatitis B. N Engl J Med 352; 26: 2682-2695.	RCT - Partially double blind.	n=814 271 patients received 100 mg lamivudine once daily for 48 weeks, 271 received peginterferon α-2a + lamivudine and 272 received 180 µg of peginterferon α-2a once weekly+ oral placebo once daily for 48 weeks.	Patients with HBeAg-positive chronic hepatitis B. Incluson: adults were eligible if they had been positive for hepatitis B surface antigen (HBsAg) for at least 6 months, were negative for antibodies to HBsAg and positive for HBeAg, had an HBV DNA level of more than 500,000 copies per millilitre, had a serum alanine aminotransferase level that was greater than 1 but less than or equal to 10 times the upper limit of the normal range, and had had findings on a liver biopsy within the previous 12 months that were consistent with the presence of chronic hepatitis B. Setting: Multi centre (67 sites in 16 countries in Asia, Australia, Europe, and North and South America) Exclusion criteria: decompensated liver disease, a co-existing serious medical or psychiatrist illness, a neutrophil count of less than 1500 per cubic millilitre, a platelet count of less than 90,000 per cubic millilitre, a serum creatinine level that was more than 1.5 times the upper limit of the normal range, a history of alcohol or drug abuse within one year before entry, and co-infection with hepatitis C or D virus or IV virus. Previous treatment fro chronic hepatitis B was permitted, but not within the 6 months before the study. Baseline characteristics Characteristic | Lamivudine (n=272) | Peg IFN α-2a + placebo (n=271) | Peg IFN α lamivudir (n=271)	Genotype B versus C (numbers were too small for the genotypes A, D to allow analysis) No multivariable analysis	Week 48 (end of treatment) and week 72 (end of 24 weeks follow-up)	HBeAg seroconversion (HBeAg loss and presence of anti-Hbe antibodies)	Roche, Basel, Switzerland.

			Male sex- no (%)	215 (79)	214 (79)	208 (77)				
			Age (yr) mean±SD	31.6±9.7	32.5±9.6	31.7±10.3				
			Alanine aminotransferase-IU/litre mean±SD	102.3±78.4	114.6±114.3	114.9±94				
			HBV DNA-log copies/ml mean±SD	10.1±2.0	9.9±2.1	10.1±1.9				
			Bridging fibrosis or cirrhosis- no (%)	47 (17)	49 (18)	40 (15)				
			Previous use of conventional interferon alpha- no (%)	32 (12)	30 (11)	32 (12)				
			Previous use of lamivudine- no (%)	42 (15)	31 (11)	24 (9)				
			Genotypes							
			-A	15 (6)	23 (8)	18 (7)				
			-B	73 (27)	76 (28)	82 (30)				
			-C	162 (60)	162 (60)	156 (58)				
			-D	17 (6)	9 (3)	11 (4)				
			-E,F or H	4 (1)	0	3 (1)				
			-Mixed	1 (<1)	1 (<1)	1 (<1)				

Results:

HBeAg seroconversion at 72 weeks	Genotype A	Genotype B	Genotype C	Genotype D
On Peg IFN α-2a + placebo treatment (N=271)	12/23	23/76	50/162	2/9
On Peg IFN α-2a + lamivudine treatment (N=271)	4/18	24/82	43/156	2/11
On lamivudine treatment (N=272)	3/15	17/73	29/162	3/17

Authors' conclusion:

Nothing was related to genotypes in the study.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Janssen HLA, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, Simon C, So TMK, Gerken G, de Man R, Niesters	RCT double blinded.	N= 307 (152 and 155 patients were randomised to peg α-2b + lamivudine and peg alpha 2b + placebo respectively for 52 weeks). 266	Setting: 42 centres in 15 countries in Europe, East Asia, North America. Inclusion: Aged 16 or older; Positive for HBsAg > 6 months; positive for HBeAg on at least 2 occasions within 8 weeks before randomisation; at least 2 episodes of raised ALT (2x ULN) within the 8 weeks prior to randomisation. Exclusion: Hep C, Hep D or HIV antibodies; antiviral or immunosuppressive therapy in the last 6 months; pregnancy or inadequate contraception; substance abuse within last 2 years; other causes of liver disease;	Genotypes A vs B vs C vs D. Multivariable analysis conducted based on full set of baseline characteristics; method of regression analysis not stated	78 weeks (26 weeks post Rx cessation).	Sustained response defined as serum HBeAg loss at the end of follow up (78 weeks)	Schering-Plough International ; GlaxoSmithKline. Each centre run by an independent company.

HGM, Zondervan P, Hansen B, Schalm SW. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. The Lancet 2005; 365: 123-129.		patients were included in the final analysis.	co-existing serious mental illness; uncontrolled thyroid disease; low leucocyte (<3x109/L), granulocyte (<1.8x109/L) or platelet (<100 x109/l) counts; liver ca; advanced liver disease with prothrombin time prolonged > 3 secs, serum albumi <35 g/L, bilirubin >35 micromol/L, or a history of ascites, variceal bleeding, or hepatic encephalopathy. Baseline characteristics: Characteristics described as "similar": Mean age (sd): 34(12) / 36(14) Mean weight (sd), kg: 74(16) / 72(13) Sex (% men): 75% / 79% Mean serum HBV DNA (sd), log10 copies/ml: 9.1(1) / 9.1(0.8) Mean serum ALT (sd), U/L: 4.4(3.9) / 4.3(3.1) Previous interferon therapy: 27/130 / 28/136 Previous LAM therapy: 17/130 / 16/136 Previous cirrhosis: 13 (12%) / 11 (10%) Ethnicity white: 95/130 / 101/136 asian: 24/130 / 29/136 other/mixed: 11/130 / 6/136 Genotypes				

			-A	43 (33%)	47 (35%)				
			-B	11 (9%)	12 (9%)				
			-C	18 (14%)	21 (15%)				
			-D	52 (40%)	51 (38%)				
			-Other	6 (4%)	5 (4%)				

Results:

	Genotype A	Genotype B	Genotype C	Genotype D
Sustained response (at the end of 26 weeks follow up)* (N=266)	42/90 (47%)	10/23 (44%)	11/39 (28%)	26/103 (25%)

The authors reported that because HBeAg loss (sustained response) at the end of follow up was similar between the two groups (35% and 36% for the combined and monotherapy groups respectively, they presented the analysis of the genotypes for the whole sample.

Multivariable analysis:

For sustained response at week 26 post-treatment (n=89 events), the analysis included about 17 predictors - age, gender, weight, ethnicity (White, Asian, Other/mixed), HBV transmission (vertical, sexual/parenteral, unknown), ALT, HBV DNA, HBV genotype (A, B, C, D, other), history of cirrhosis, history of previous interferon therapy, previous lamivudine therapy ; i.e. events/covariate = 5.2. Results were:

- Genotype A versus C: OR 3.6 (95%CI 1.4 to 8.9); p=0.006; 11/39 (28%) response rate for Genotype C
- Genotype A versus D: OR 2.4 (95%CI 1.3 to 4.6); p=0.01; 26/103 (25%) response rate for Genotype D
- Genotype B versus C: OR 2.2 (95%CI 0.7 to 7.0); p=0.18; 11/39 (28%) response rate for Genotype C
- Low viral load (not defined): OR 1.6 (95%CI 1.3 to 1.8); p=0.009
- High ALT levels (not defined): OR 1.1 (95%CI 1.0 to 1.2); p=0.02
- Absence of previous interferon therapy: OR 2.2 (95% 1.1 to 4.5); p=0.04

Authors' conclusion:.HBV genotype is an important predictor of response to treatment.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Sonneveld MJ, Rijckborst V, Zeuzem S, Heathcote EJ, Simon K, ,Senturk H, Pas SD, , Hansen B, Janssen HLA, Presence of precore and core promoter mutants limits the probability of response to peginterferon in hepatitis B e antigen-positive chronic hepatitis B. Hepatology 2012	RCT double blinded (Janssen 2005).	N= 307 (152 and 155 patients were randomised to peg α-2b + lamivudine and peg alpha 2b + placebo respectively for 52 weeks). 266 patients were included in the final analysis for the Janssen study and of these, 214 had a baseline serum sample for precore and basal core promoter mutant assessment	Setting: 42 centres in 15 countries in Europe, East Asia, North America. Inclusion: Aged 16 or older; Positive for HBsAg > 6 months; positive for HBeAg on at least 2 occasions within 8 weeks before randomisation; at least 2 episodes of raised ALT (2x ULN) within the 8 weeks prior to randomisation. Exclusion: Hep C, Hep D or HIV antibodies; antiviral or immunosuppressive therapy in the last 6 months; pregnancy or inadequate contraception; substance abuse within last 2 years; other causes of liver disease; co-existing serious mental illness; uncontrolled thyroid disease; low leucocyte (<3x109/L), granulocyte (<1.8x109/L) or platelet (<100 x109/l) counts; liver ca; advanced liver disease with prothrombin time prolonged > 3 secs, serum albumi <35 g/L, bilirubin >35 micromol/L, or a history of ascites, variceal bleeding, or hepatic encephalopathy. Baseline characteristics: Characteristics described as "similar":	Genotypes A vs B vs C vs D. Multivariable analysis conducted based on full set of baseline characteristics; method of regression analysis not stated	78 weeks (26 weeks post treatmen t cessation).	Composite response defined as serum HBeAg loss and HBV DNA level <10,000 copies per ml at the end of follow up (78 weeks)	Schering-Plough International ; GlaxoSmithK line. Each centre run by an independent company.

	Peg alpha 2b + LAM (n=130)	Peg alpha 2b (n=136)
Mean age (sd)	34(12)	36(14)
Mean weight (sd), kg	74(16)	72(13)
Sex (% men)	75%	79%

online issue.			Mean serum HBV DNA (sd), log10 copies/ml	9.1(1)	9.1(0.8)				
			Mean serum ALT (sd), U/L	4.4(3.9)	4.3(3.1)				
			Previous interferon therapy	27/130	28/136				
			Previous LAM therapy	17/130	16/136				
			Previous cirrhosis	13 (12%)	11 (10%)				
			Ethnicity						
			white	95/130	101/136				
			asian	24/130	29/136				
			other/mixed	11/130	6/136				
			Genotypes						
			-A	43 (33%)	47 (35%)				
			-B	11 (9%)	12 (9%)				
			-C	18 (14%)	21 (15%)				
			-D	52 (40%)	51 (38%)				
			-Other	6 (4%)	5 (4%)				

Results:

The authors reported that because HBeAg loss (sustained response) at the end of follow up was similar between the two groups (35% and 36% for the combined and monotherapy groups respectively, they presented the analysis of the genotypes for the whole sample.

Multivariable analysis:

For composite response at week 26 post-treatment (n=41 events), the analysis included predictors determined previously plus wild type status: ALT, HBV DNA, HBV genotype (A, B, C, D), age, presence of wild type (wild type virus versus non-WT (detectable PC and/or BCP mutants) ; i.e. events/covariate = 5.9. Results were:

- Genotype B versus A: OR 0.56 (95%CI 0.14 to 2.21); number of events for each genotype not stated
- Genotype C versus A: OR 0.11 (95%CI 0.02 to 0.59)
- Genotype D versus A: OR 0.35 (95%CI 0.11 to 1.14)

- WT versus non WT: OR 2.90 (95%CI 1.15 to 7.31); p=0.023
- HBV DNA: OR 0.58 (95%CI 0.35 to 0.97) per log10 copies/ml; p=0.038
- ALT: OR 1.10 (95%CI 0.95 to 1.26) per1xULN; p=0.210
- Age 1.04 (95%CI 1.01 to 1.08) per year; p=0.014
- Absence of previous interferon therapy: OR 5.20 (95% 1.55 to 17.4); p=0.003

Authors' conclusion:.HBV genotype is an important predictor of response to treatment.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Flink 2006. Treatment with Peg-Interferon α-2b for HBeAg positive Chronic Hepatitis B: HbsAg loss is associated with HBV Genotype. American Journal of Gastroenterology 2006; 297- 303. There was no	RCT double blinded (Janssen 2005)	N= 307 (152 and 155 patients were randomised to peg α-2b + lamivudine and peg alpha 2b + placebo respectively for 52 weeks). 266 patients were	Setting: 42 centres in 15 countries in Europe, East Asia, North America. Inclusion: Aged 16 or older; Positive for HBsAg > 6 months; positive for HBeAg on at least 2 occasions within 8 weeks before randomisation; at least 2 episodes of raised ALT (2x ULN) within the 8 weeks prior to randomisation. Exclusion: Hep C, Hep D or HIV antibodies; antiviral or immunosuppressive therapy in the last 6 months; pregnancy or inadequate contraception; substance abuse within last 2 years; other causes of liver disease; co-existing serious mental illness; uncontrolled thyroid disease; low leucocyte (<3x109/L), granulocyte (<1.8x109/L) or platelet (<100 x109/l) counts; liver ca; advanced liver disease with prothrombin time prolonged > 3 secs, serum albumi <35 g/L, bilirubin >35 micromol/L, or a history of ascites, variceal bleeding, or hepatic encephalopathy.	Genotypes A vs B vs C vs D. No multivariable analysis	78 weeks (26 weeks post Rx cessation).	1)Loss of HBeAg without loss of HbsAg at the end of follow up (78 weeks) 2)Loss of both HBeAg and HbsAg at the end of follow up (78 weeks)	By the foundation for Liver Research (SLO), Rotterdam, The Netherlands. Financial support and study medication was provided

multivariable analysis		included in the final analysis (same patients as those included in the study by Janssen 2005)					by Schering-Plough International, Kenilworth, NJ, USA and GlaxoSmithKline, Research and Development, Greenford, UK.

Baseline characteristics

Characteristic	Genotype A (n=90)	Genotype B (n=23)	Genotype C (n=39)	Genot D (n=
Age (yr) mean±SD	43±14.1	33±8.1	35±10	29±10
Weight (kgr)	77±12.8	64±10.1	68±11.8	74±15
ALT (xULN)	4.2±2.6	4.2±2.2	3.9±2.8	4.6±4
Log HBV DNA	9.1±0.8	8.3±1.4	8.3±0.9	9.5±0
Histology				
-Fibrosis	3 (0-6)	3 (0-6)	3 (0-6)	3 (0-6
- Necroinflammation	6 (2-10)	6 (3-8)	5 (2-10)	4 (1-1
Race (%)				
-Caucasian	87 (97%)	1 (4%)	2 (5%)	98 (95
-Asian/ Mongoloid	1 (1%)	18 (78%)	31 (80%)	0
-Others	2 (2%)	4 (17%)	6 (15%)	5 (5%
Area of enrollment (%)				
- North&West Europe	55 (61%)	7 (30%)	12 (31%)	24 (23
-Eastern Europe	28 (31%)	0	0	2 (2%
- Mediteraranean	5 (6%)	0	0	77 (75

			-East Asia -North America	0 2 (2%)	11 (48%) 5 (22%)	17 (44%) 10 (26%)	0 0			

Results:

	Genotype A	Genotype B	Genotype C	Genotype D
HBeAg loss but not HbsAg loss (at the end of 26 weeks follow up)* (this was defined as sustained respose in the study by Janssen et al, 2005) (N=266)	42/90 (47%)	10/23 (44%)	11/39 (28%)	26/103 (25%)
HBeAg and HbsAg loss (at the end of 26 weeks follow up)* (N=266)	13/90 (14%)	2/23 (9%)	1/39 (3%)	2/103 (2%)

The authors reported that because HBeAg loss (sustained response) at the end of follow up and HbsAg loss were similar between the two groups (HBeAg loss: 35% and 36% for the combined and monotherapy groups respectively, 7% of both groups experienced HbsAg loss at the end of follow up) they presented the analysis of the genotypes for the whole sample.

Authors' conclusion: The authors concluded that their study indicated that treatment with peg-interferon α-2b is the best therapy to achieve HbsAg clearance in patients with genotype A.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Buster 2008A. Sustained HBeAg and HbsAg Loss	Long term follow up from a	N= 307 (152 and 155 patients	Setting: 42 centres in 15 countries in Europe, East Asia, North America. Inclusion: Aged 16 or older; Positive for HBsAg >	Genotypes A vs B vs C vs D only for initial responders (achieved HBeAg loss at the end of 78 week at the	Mean follow up 3+/- 0.8 years	HBeAg loss HBV DNA<400 copies/ml	None mentioned

after Long-term Follow-up of HBeAg – Positive Patients Treated with Peginterferon α-2b. Gastroenterology 2008; 135: 459-467.	double blinded RCT (Janssen 2005)	were initially randomised to peg α-2b + lamivudine and peg alpha 2b + placebo respectively for 52 weeks). 266 patients were included in the final analysis (same patients as those included in the study by Janssen 2005). 172/266 (65%) patients participated in this follow up study. Patients did not enrol in this follow	6 months; positive for HBeAg on at least 2 occasions within 8 weeks before randomisation; at least 2 episodes of raised ALT (2x ULN) within the 8 weeks prior to randomisation. Exclusion: Hep C, Hep D or HIV antibodies; antiviral or immunosuppressive therapy in the last 6 months; pregnancy or inadequate contraception; substance abuse within last 2 years; other causes of liver disease; co-existing serious mental illness; uncontrolled thyroid disease; low leucocyte (<3x109/L), granulocyte (<1.8x109/L) or platelet (<100 x109/l) counts; liver ca; advanced liver disease with prothrombin time prolonged > 3 secs, serum albumi <35 g/L, bilirubin >35 micromol/L, or a history of ascites, variceal bleeding, or hepatic encephalopathy. Baseline characteristics Characteristic | Initial study (n=266) (Janssen, 2005) | Present follow up study (n=172) Start of the treatment Peg-IFN monotherapy | 136 (51%) | 91 (53%) Age (yr) mean±SD | 35±12.9 | 35.5±13.3 Male, n (%) | 207 (78%) | 137 (80%) Ethnicity -White | 196 (74%) | 124 (72%) -Asian | 53 (20%) | 35 (20%) -Other | 17 (6%) | 13 (8%)	study by Janssen et al, 2005) Statistical analysis: the study conducted a Cox regression analysis and identified baseline factors associated with an increased risk of HBeAg relapse after the initial study. Baseline factors (univariate analysis) associated with this were: 1. Younger age: HR 0.93 (95%CI 0.87 to 0.99) per year age 2. HBV genotype non-A versus A: HR 11.84 (95%CI 1.50 to 93.7) 3. Elevated ALT (assumed continuous): HR 5.10 (95CI 1.53 to 17.03) 4. High HBV DNA level: HR 1.57 (95%CI 1.21 to 2.04) per 1 log10 increase Multivariable analysis was stated to be not possible due to the small number of events for sustained HBeAg seroconversion (n=53)	(range 1.6-5 years) after the end of initial study	HbsAg loss	

		up study as the local study site did not for several reasons (n=52) or they were lost to follow up (n=23)	ALT (xULN)	4.3±3.5	4.7±4.0			
			Log HBV DNA	9.1±0.9	9.0±0.9			
			Genotypes -A -B -C -D -Other	 90 (34%) 23 (9%) 39 (15%) 103 (39%) 11 (4%)	 53 (31%) 13 (8%) 32 (19%) 66 (38%) 8 (5%)			
			Necroinflammation (median)	5 (1-10)	5 (1-10)			
			Fibrosis	3 (0-6)	3 (0-6)			
			26 weeks post treatment (end of initial study)					
			HBeAg loss	95 (36%)	64 (37%)			
			HBeAg seroconversion	77 (29%)	53 (31%)			
			HBV DNA<400 copies/ml	21 (8%)	14 (8%)			
			ALT normalization	92 (37%)	61 (36%)			
			HbsAg loss	18 (7%)	12 (7%)			
			HbsAg seroconversion	16 (6%)	11 (6%)			

Results:

	Genotype A (n=26)	Genotype B (n=7)	Genotype C (n=9)	Genotype D (n=17)
HBeAg loss at the end of long term follow up (N=172)	25/26 (96%)	6/7 (86%)	6/9 (67%)	13/17 (76%)
HBV DNA<400 copies/ml at the end of long term follow	17/26 (65%)	2/7 (29%)	3/9 (33%)	4/17 (24%)

up (N=172)				
HbsAg loss at the end of long term follow up (N=172)	15/26 (58%)	1/7 (14%)	0/9 (0%)	1/17 (6%)

Authors' conclusion: HBeAg loss after treatment with Peg-IFN α-2b alone or in combination with lamivudine is sustained in the majority of patients and is associated with a high likelihood of HbsAg loss, particularly in genotype A-infected patients.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Flink 2005. Flares in chronic hepatitis B induced by the host or the virus? Relation to treatment response during Peg-interferon α-2b therapy. Gut 2005: 54; 1604-1609.	RCT double blinded (Janssen 2005)-	N= 307 (152 and 155 patients were randomised to peg α-2b + lamivudine and peg alpha 2b + placebo respectively for 52 weeks). Among the 266 patients analyzed (same patients as those	Setting: 42 centres in 15 countries in Europe, East Asia, North America. Inclusion: Aged 16 or older; Positive for HBsAg > 6 months; positive for HBeAg on at least 2 occasions within 8 weeks before randomisation; at least 2 episodes of raised ALT (2x ULN) within the 8 weeks prior to randomisation. Exclusion: Hep C, Hep D or HIV antibodies; antiviral or immunosuppressive therapy in the last 6 months; pregnancy or inadequate contraception; substance abuse within last 2 years; other causes of liver disease; co-existing serious mental illness; uncontrolled thyroid disease; low leucocyte (<3x109/L), granulocyte (<1.8x109/L) or platelet (<100 x109/l) counts; liver ca; advanced liver disease with prothrombin time prolonged > 3 secs, serum albumi <35 g/L, bilirubin >35 micromol/L, or a history of ascites, variceal bleeding, or hepatic encephalopathy.	Genotypes A vs B vs C vs D only for patients with flares (defined as a threefold increase in serum ALT compared with baseline levels- the time point of the flare was defined as the time of the peak level of serum ALT). HBV genotype was assessed by Inno-Lipa assay. Statistical analysis: for the outcome response to treatment in the flare population (20/67 events, 10 each for monotherapy and combination therapy), multivariable Cox regression analysis was conducted. Variables significant on univariate	78 weeks (26 weeks post Rx cessation).	Response to treatment was defined as serum HBeAg loss at the end of follow up.	By the foundation for Liver Research (SLO), Rotterdam, The Netherlands. Financial support and study medication was provided by Schering-Plough International,

		included in the study by Janssen 2005) 75 flares were recorded in 67 patients and were the focus of this study.	Baseline characteristics of patients who had a flare, according to therapy Characteristics / Peg-IFN placebo (n=32 (48%)) / Peg-IFN lamivudine (n=35 (52%)) Male sex- no (%) / 24 (75%) / 28(80%) Age (yr) Mean (SD) / 36 (13.1) / 33 (10.8) Race / / -Caucasian / 21 (66%) / 26 (74%) -Asian/ Mongoloid / 7 (22%) / 6 (17%) ALT (x ULN) Mean (Sd) / 2.9 (1.3) / 2.9 (1.5) Log HBV DNA Mean (SD) / 8.9 (1.3) / 9.2 (0.9) Genotype (%) / / -A / 9 (28%) / 10 (29%) -B / 2 (6%) / 5 (14%) -C / 7 (22%) / 4 (11%) -D / 11 (34%) / 15 (43%) Pre existing cirrhosis (%) / 5 (16%) / 5 (14%) Discontinuation of treatment (%) / 4 (13%) / 5 (14%) Flares during treatment / 20 (63%) / 14 (40%) Time of flare Median (range) / 36 (4-78) / 60 (4-78) Response (%) / 10 (31%) / 10 (29%)	analysis (p<0.15) were included in the analysis: results not stated and unclear which variables were entered			Kenilowrth, NJ, USA and GlaxoSmithKline, Research and Development, Greenford, UK.

Results :
Flares were observed in similar proportions of patients who received monotherapy (48%) and combination therapy (52%)

	Genotype A (n=19)	Genotype B (n=7)	Genotype C (n=11)	Genotype D (n=26)
Response to treatment (HBeAg loss at the end of follow up) (N=67)	9/19 (47%)	2/7 (28%)	2/11 (18%)	5/26 (19%)

Authors' conclusion: In addition to the timing of flares, response to treatment was dependent on HBV genotype and the magnitude of the flare.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Sonneveld 2012B. Durable hepatitis B surface antigen decline in hepatitis B e antigen-positive chronic hepatitis B patients treated withh pegylated	Long term follow up from a double blinded RCT (Janssen 2005) and a subsequent folllow up	N= 307 (152 and 155 patients were initially randomised to peg α-2b + lamivudine and peg alpha 2b + placebo respectively for 52 weeks). 266 patients were	Setting: 42 centres in 15 countries in Europe, East Asia, North America. Inclusion criteria for the initial RCT (Janssen 2005): Aged 16 or older; Positive for HBsAg > 6 months; positive for HBeAg on at least 2 occasions within 8 weeks before randomisation; at least 2 episodes of raised ALT (2x ULN) within the 8 weeks prior to randomisation. Further inclusion criteria for this study: completion of the 26 week follow up phase of the main study and availability of a baseline serum sample for HbsAg quantification.	Genotypes A vs B vs C vs D. HBV genotype was assessed by Inno-Lipa assay. Statistical Analysis: multivariable analysis not conducted	Mean duration was 3 years.	Response to treatment was assessed at week 78 in all patients. Compine response was defined as HBeAg loss and HBV DNA<10,000 copies/ml. HBeAg response was defined as HBeAg loss but failure to achieve HBV DNA<10,000 copies/ml	By the foundation for Liver Research (SLO), Rotterdam, The Netherlands.

interferon-a2b: relation to response and HBV genotype.	study (Buster 2008).	included in the final analysis (same patients as in Janssen 2005 study). 221 completed the 26 week follow up of the main phase and had available baseline serum sample for HbsAg quantification and were included for this study. Of these patients 142 participated in the associated long term follow up study (Buster 2008) and had available samples for HbsAg quantification.	Exclusion: Hep C, Hep D or HIV antibodies; antiviral or immunosuppressive therapy in the last 6 months; pregnancy or inadequate contraception; substance abuse within last 2 years; other causes of liver disease; co-existing serious mental illness; uncontrolled thyroid disease; low leucocyte (<3x109/L), granulocyte (<1.8x109/L) or platelet (<100 x109/l) counts; liver ca; advanced liver disease with prothrombin time prolonged > 3 secs, serum albumi <35 g/L, bilirubin >35 micromol/L, or a history of ascites, variceal bleeding, or hepatic encephalopathy. Baseline characteristics				

Characteristic	Main study population (n=221)	Follow up study population (n=142)
Male sex- no (%)	173 (78%)	115 (81%)
Age (yr) mean±SD	34±12	34±12
Monotherapy	111 (50%)	75 (50%)
Race -Caucasian -Asian/ Mongoloid -Other	 160 (72%) 44 (20%) 17 (8%)	 99 (70%) 30 (21%) 13 (9%)
ALT (x ULN) Mean (SD)	4.2 (3.0)	4.6 (3.4)
Log HBV DNA Mean (SD)	9.1 (0.89)	9.1 (0.80)

HbsAg, log IU/ml Mean (SD)	4.4 (0.64)	4.3 (0.69)
Genotype (%) -A -B -C -D -Other/mixed	 74 (34%) 20 (9%) 32 (15%) 87 (39%) 8 (4%)	 41 (29%) 12 (9%) 27 (19%) 56 (39%) 6 (4%)
Response at week 78 -combined response - HBeAg loss, n (%) -HbsAg loss, n (%)	 43 (19%) 84 (38%) 19 (9%)	 24 (17%) 49 (35%) 10 (7%)

Results:

	Genotype A (n=41)	Genotype B (n=12)	Genotype C (n=27)	Genotype D (n=56)
Combined response to treatment (HBeAg loss and HBV DNA<10,000 copies/ml) (N=43)	28 (68%)	5 (42%)	3 (11%)	6 (11%)
HBeAg response to treatment (HBeAg loss but not HBV DNA<10,000 copies/ml) (N=41)	9 (22%)	5 (42%)	5 (19%)	18 (32%)

Authors' conclusion: patients with a combined response to Peg IFN therapy for HBeAg positive CHB depends upon HBV genotype, which is sustained through 3 years off treatment follow up.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Cooksley 2003. Peginterferon α-2a (40kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. Journal of Viral Hepatitis 2003: 10; 298-305.	Open label multicentre phase II study comparing the efficacy and safety of three different dosages of peginterferon α-2a with that of conventional interferon α-2a. Treatment was provided for 24 weeks.	N=194	Adults (>=18 years of age) with HBeAg-positive chronic hepatitis B who had not previously treated with conventional interefon, HbsAg positive for more than 6 months, HBV DNA> 500,000 copies/ml, elevated serum ALT value 2-10 times the upper limit of normal (ULN), a liver biopsy demonstarating liver disease consistent with CHB, and negative urine or serum pregnancy test. In addition, all fertile men with partners of childbearing age and premenopausal woment were required to use reliable contraception during the study and for 3 months after treatment completion. Patients with cirrhosis or transition to cirrhosis on liver biopsy must also have had a liver imaging study to rule out hepatic carcinoma. Setting: 18 centeres in Australia, New Zealand, Taiwan, Thailand, and China. Exclusion criteria: nucleoside or nucleotide analogue use for longer than 6 months and/or within 5 months of study entry; other systemic antiviral therapy; positive test at screening for anti-HAV IgM, HCV RNA or anti-HCV, anti-HDV or anti-HIV; an increased risk of metabolic liver disease other than viral hepatitis; pregnancy or breast-feeding; alcohol or drug abuse within 1 year of entry; history of severe psychiatric	Genotypes B versus C. Multivariable analysis was not conducted	24 weeks after the end of treatment	Combined response was defined as HBeAg loss, suppression of HBV DNA <500,000 copies/ml and normalization of ALT.	None mentioned

disease or immunologically mediated disease; bleeding from esophageal varices or other conditions consistent with decompensated liver disease; severe cardiac or chronic pulmonary disease; severe seizure disorder or current anticonvulsant use; active or suspected cancer or a history of malignancy where the risk of recurrence is >=20% within 2 years; history of antineoplastic or immunomodulatory treatment including systemic corticosteroids; major organ transplantation; thyroid disease; severe retinopathy and a history of other severe illnesses or conditions.

Baseline characteristics

Characteristic	Interferon (n=51)	Peginterferon α 2a (all groups) (n=143)
Male sex- o (%)	38 (75%)	105 (73.4%)
Age (yr) Mean (range)	30.6 (19-53)	18-69)
Race -Asian -Other	 -48 (94%) -3 (6%)	 -93 (65%) -50 (35%)
Family history of HBV infection, n(%) -Yes -No -Unknown	 -19 (37%) -17 (33%) -15 (29%)	 -48 (34%) -53 (37%) -42 (29%)
Cirrhosis, n(%)	4 (8%)	13 (9%)
Log10 HBeAg (PEIU/ml), mean (SE)	2.57 (0.19)	2.70
Log10 HBV DNA (copies/ml), mean	9.2 (0.19)	9.3

			(SE)					
			ALT (U/L), mean (SE)	114.5 (9.8)	139.3			

Results:

	Genotype B (n=125)	Genotype C (n=61)
Combined response to Peg interferon treatment (N=143)	41 (33%)	13 (21%)
Combined response to interferon treatment (N=51)	31 (25%)	4 (6%)

Authors' conclusion: none related to genotypes.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Chen 2011. Hepatitis B virus genotype B results in better immediate, lat and sustained responses to peginterferon-alpha in hepatitis B e antigen positive patients. Journal of Gastroenterol	Follow up study.	N=88	Patients with HBeAg-positive chronic hepatitis B, who (as part of the study) received peginterferon α-2a (180µg) weekly for 6 months, after which they were followed for 24 weeks 48/88 (55%) were genotype B Inclusion: seropositivity for HbsAg for at least 6 months prior to entry, seropositivity for HBeAg and HBV DNA>105 copies/ml and elevation of serum alanine aminotransferase (ALT) levels two times above the upper limit of normal (40 U/L) before therapy. Setting: Taiwan Exclusion criteria: any sign of autoimmune hepatitis, markers of HCV, HDV, or HIV, previous oral antiviral drug treatment for CHB in the last six months.	Genotypes B versus C Statistical analysis: Multivariable logistic regression for all baseline characteristics was conducted for HBeAg clearance at24 weeks post treatment (34 events); and	24 weeks after the end of peginterferon treatment	HBeAg clearance was defined as the loss of HBeAg with or without anti-HBe on at least two consecutive follow up visits 4 weeks apart. HBeAg seroconversion was as HBeAg loss with anti-HBe as above Combined	By a grant CMRPG 880011 from Chang Gung Memorial Hospital.

ogy and Hepatology 2011: 26; 461-468.			Baseline (pre-treatment) characteristics Characteristic: Total sample (N=88) Male:female: 69:19 Age (yr) mean±SD: 35.1 (8.4) ALT (U/L): <=200: 34 (38%) >200: 54 (62%) (Cut-off from ROC curve) HBV DNA (copies/ml) <=108: 52 (59%) >108: 36 (41%) (Cut-off from ROC curve)	for HBeAg seroconversion (32 events).		response was defined as serum HBV DNA level below 105 copies/ml, HBeAg seroconversion, and normal ALT level at 24 weeks post treatment.	

Results:

	Genotype B (n=48)	Genotype C (n=40)
HBeAg loss (N=34)	25 (52%)	9 (23%)
Combined response (N=25)	20 (42%)	5 (13%)

The authors also reported that univariate analysis revealed that genotype B was important factor for delayed HBeAg seroconversion (P-0.012) after 24 week post treatment.

Multivariable analysis:

For HBeAg clearance at week 24 post-treatment (n=34 events), the analysis included 9 predictors - age, gender, ALT ≤200, T-bilirubin, HBeAg pretreatment sample: cutoff ratio ≤200, HBV DNA≤ 8 log10 copies, genotype B vs C, T1846 mutation, A1896 mutation; i.e. events/covariate = 3.8. Results were significant for:

- Genotype B versus C: OR 4.4 (95%CI 1.2 to 16.1); 9/40 (23%) response rate for Genotype C
- HBeAg S/Co ratio ≤200 versus >200: OR 20.4 (95%CI 5.2 to 83.3)
- ALT > 200 versus ≤200 U/l: OR 3.7 (95%CI 1.04 to 13.4)
- T1846 mutation at baseline: OR 4.2 (95% 1.01 to 17.5)

For HBeAg seroconversion at week 24 post treatment (n=32 events), multivariable significant predictors were HBeAg S/Co ratio ≤200 versus >200 and T1846 mutation, i.e. Genotype was not a significant predictor (but no data)

For the combined response at week 24 post treatment (n=25 events; ratio events:covariates =2.8), multivariable significant predictors were:

- Genotype B versus genotype C: OR 7.2 (95%CI 2.1 to 25)
- HBeAg S/Co ratio ≤200 versus >200: OR 8.6 (95%CI 2.7 to 27)

Authors' conclusion: HBV genotype B was a significant factor to predict both HBeAg clearance and combined response for patients treated with peginterferon α-2a.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Fan HB, Guo YB, Zhu YF, Chen AS, Zhou MX, Li Z, Xu LT, MA XJ, Yan FM. HepatitisB virus genotype B and high expression of interferon alpha receptor β subunit are associated with better response to pegylated interferon alpha 2a in Chinese patients with chronic hepatitis B	Follow up study.	N=65 but 5 people did not complete treatment because of severe adverse events	Outpatients with HBeAg-positive or negative chronic hepatitis B received peginterferon α-2a (180µg) weekly for 6 months, after which they were followed for 24 weeks. 33/60 (55%) were genotype B Inclusion: "Chronic hepatitis B infection". Exclusion: patients with infections caused by other viruses, including hepatitis C, D, A and E; HIV; autoimmune hepatitis, patients with liver cirrhosis, decompensated liver disease, current/past history of alcohol abuse, psychiatric conditions, previous liver transplantation, evidence of HCC and patients who were taking antiviral drugs or interferon before biopsy.. Setting: China Baseline (pre-treatment) characteristics Characteristic: Total sample (N=52) Male:female: 33:19 Age (yr) mean±SD: 31.5 (8)	Genotypes B versus C Statistical analysis: Multivariable forward stepwise logistic regression, including all factors that had a p-value of <0.05 in univariate analysis (n=30 events)	24 weeks after the end of peginterferon treatment	Sustained composite viral response defined as continued response after cessation of treatment for normalisation of ALT and HBV DNA loss.	Stated to be "none declared"

infection. Hepat. Mon. 2012: 12; 333-8.			HBeAg positivity	Genotype B: 20 (60.6%) Genotype C: 14 (73.7%)			
			Genotype distribution B C B+C D	 33 (55.0%) 19 (31.7%) 3 (5.0%) 3 (5.0%)			
			ALT (U/L)	Genotype B: 163.5 (SD 97.5); C 134.0 (SD 59.6)			
			HBV DNA (log10 copies/ml)	9.3 (SD 2)			

Results:

	Genotype B (n=33)	Genotype C (n=19)
Sustained combined response (N=30)	22 (66.7%)	5 (26.3%)

Multivariable analysis:

For composite sustained response at week 24 post-treatment (n=30 events), the analysis included 6 predictors – IFNAR2 expression in the liver, ALT level, ,age, gender,, HBeAg status, Genotype, HBV DNA level; i.e. events/covariate = 5 Results were significant for:

- IFNAR2 expression in the liver: OR 3.80 (95%CI 2.54 to 5.7); p<0.05
- ALT level: OR 1.05 (95%CI 1.03 to 1.08) per U/L; p<0.05
- HBV DNA level <5 log10 copies/ml versus ≥ 5 log10: OR 1.75 (95%CI 1.14 to 2.56); p< 0.05
- Genotype B versus C: not significant

Authors' conclusion: HBV genotype B and high expression of IFNAR2 in the liver are closely associated with better response to Peg-IFN- α-2a therapy among Chinese patients with chronic hepatitis B.

Reference	Study type	Number of	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of

		patients					**funding**
Bonino 2007. Predicting response to peginterferon α-2a, lamivudine and the two combined for HBeAg negative chronic hepatitis B. Gut 2007: 56; 699-705.	Roll over long term observational study	N=537 analyzed in the original RCT (Marcellin, 2004). For the analysis of this study only those of Asian or Caucasian origin and singularly infected with HBV genotype A, B, C or D were included (N=518).	Patients with HBeAg-negative chronic hepatitis B who participated in a trial comparing peginterferon α-2a monotherapy versus peginterferon α-2a plus lamivudine versus lamivudine monotherapy for 48 weeks (Marcellin, 2004). Inclusion: positivity for HBsAg and anti-HBe antibody but negative for HBeAg, HBV DNA level> 100,000 copies/ml and an ALT level>1 times but <=10 times the upper limit of normal (ULN; 30 IU/l in this study). All patients included had CHB status confirmed by liver biopsy within 12 months prior to randomisation. Previous treatment for CHB was allowed, but not within the 6 months prior to the study. Exclusion criteria: none mentioned (linked to Marcellin 2004 study)	Genotypes A versus B versus C versus D. The authors conducted several multivariable analyses. In each case a full analysis was carried out, using pre-defined covariates and without step-up or step-down elimination. Ethnicity was later excluded because of high correlation with genotype.	1 year after the end of treatment	Post treatment combined response was defined as both ALT normalization and an HBV DNA level of <20,000 copies/ml, 24 weeks post treatment.	By a research grant from Roche, Basel, Switzerland.

Results:

	Genotype A	Genotype B	Genotype C	Genotype D
Combined response to treatment with peginterferon α-2a (N=63/172)	3/11	19/43	31/63	9/55
Proportion of all patients with given genotype	11/172 (6%)	19/172 (11%)	63/172 (37%)	55/172 (32%)
Combined response to	2/10	9/41	38/69	20/54

treatment with peginterferon α-2a treatment and lamivudine (N=68/174)				
Combined response to treatment with lamivudine (N=42/177)	1/8	19/49	15/57	7/63
Proportion with each genotype	29/523 (5.5%)	133/523 (25.4%)	189/523 (361%)	172/523 (32.9%)

Multivariable analysis:

For combined response at week 24 post-treatment in all patients across all treatments (n=173 events; n=518 patients), the analysis included 14 predictors - age, gender, genotype (4 categories), ethnicity, body weight, HAI score, serum ALT (screening and baseline), serum HBV DNA (baseline). Three treatment arms were also included and interaction terms were investigated. i.e. events/covariate >10. The results for genotype, adjusted for treatment were:

- Genotype A versus B: OR 0.42 (95%CI 0.1 to 1.2); p=0.097
- Genotype A versus C: OR 0.33 (95%CI 0.1 to 0.9); p=0.03
- Genotype A versus D: OR 0.97 (95%CI 0.3 to 2.7); p=0.958
- Genotype B versus C: OR 0.79 (95%CI 0.5 to 1.3); p=0.344
- Genotype B versus D: OR 2.31 (95%CI 1.3 to 4.2); p=0.006
- Genotype C versus D: OR 2.9 (95%CI 1.7 to 5.0); p<0.001
- For PEG interferon versus PEG IF + lamivudine: OR 1.19 (0.8 to1.9; p=0.460
- However, there was an interaction between treatment arm and genotype (p=0.018), suggesting patterns of response to the 3 study drugs differed according to genotype and the response to treatment was not uniform across the 4 genotypes

For combined response at week 24 post-treatment in the subset of patients receiving PEG interferon monotherapy or lamivudine, the interaction between treatment and genotype was no longer significant (p=0.637) indicating response for PEG interferon versus lamivudine was higher for the former, regardless of genotype.

For combined response at week 24 post-treatment in the subset of patients receiving PEG interferon monotherapy or PEG interferon + lamivudine, the interaction term was again significant (p=0.027). The authors attributed this to differing responses for the two treatments for genotypes B and D.

In this subset of patients (n=131 events), after adjusting for age, gender, body weight, screening ALT, baseline ALT and baseline HBV DNA, the comparison of PEG IF + Lamivudine versus PEG interferon monotherapy gave the following results on multivariable analysis:

- In genotype B: OR 3.5 (95%CI 1.3 to 9.1); control group risk 19/43 (44%)
- In genotype D: OR 0.4 (95%CI 0.1 to 1.2); control group risk 9/55 (16%)

For combined response at 24 weeks post-treatment in the subset of patients given PEG interferon with or without lamivudine (N=294 patients; n=139 events), multivariable analysis gave the following results:

- Genotype C versus genotype D: OR 3.3 (95%CI 1.7 to 6.5); control group risk 21%
- Age (more likely in younger patients: OR 1.3 (95%CI 1.0 to 1.7) per 10 year decrease
- HBV DNA levels at the end of treatment: OR 2.9 (95%CI 1.1 to 7.7) per 1 log10 decrease
- HBV DNA levels at baseline: OR 1.2 (95%CI 1.0 to 1.4) per 1 log 10 decrease

Authors' conclusion: infecting HBV genotype significantly influenced combined response at 24 weeks post-treatment, in patients treated with peginterferon α-2a and/or lamivudine.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Zhao 2007. Genotype B and Younger Patient Age Associated with Better Response to Low-Dose Therapy: A Trial with Pegylated/Non pegylated Interferon α-2b for Hepatitis B	Multicenter open label parallel RCT.	N=230 (equal numbers of patients randomized to pegylated IFN α-2b and IFN α-2b.	Patients with HBeAg-positive chronic hepatitis B (defined as the presence of HBsAg for at least 6 months prior to enrolment) randomized to receive pegylated IFN α-2b or IFN α-2b. Inclusion: aged 18-70 years, serum HBV DNA> 105 copies/ml, and ALT within a range of 2-10 times the upper limit of normal (ULN), WBC cound >3 x 109 platelets/L. Setting: 6 clinical centers in China. Exclusion criteria: patients with any cause of liver disease other than CHB, pregnant and/or breast	Genotypes B versus C Statistical analysis: multivariable analysis was conducted (n=29 events); treatment was also included (but not significant) no further details	24 weeks after the end of treatment.	Sustained combined response was defined as serum HBV DNA level<10^5 copies/ml, HBeAg loss and normal ALT levels at the end of 24 weeks follow up.	None mentioned.

Antigen-Positive Patients with Chronic Hepatitis in China. Clinical Infectious Diseases 2007: 44; 541-8.

feeding women, use of immune regulators during the previous 6 months, or individuals who have received antiviral treatment (nucleoside analogue and IFN) during the previous 3 months of the start of the study.

Baseline characteristics

Characteristic	Peg IFN α-2 (n=115)	IFN α-2 (n=115)
Male, no (%)	93 (80.9%)	96 (83.5%)
Age (yr) Median (range)	31 (18-53)	31 (18-66)
IFN experience	20 (17.4%)	10 (8.7%)
ALT (x ULN), mean (SD)	4.2 (2.0)	3.8 (2.0)
HBV DNA (log copies/ml), mean SD)	8.1 (0.8)	8.0 (1.0)
Genotypes -B -C	 31 (27%) 84 (73%)	 29 (25.2%) 86 (74.8%)

Results:

	Genotype B (n=60)	Genotype C (n=170)
Sustained combined response (fr both Peg IFN α-2b and IFN α-2b*) (N=29)	16 (31.7%)	13 (7.7%)
Proportion with given genotype	60/230 (26%)	170/230 (74%)

* the authors reported that there was no difference in the experience of sustained combined response between those received IFN α-2b and peg IFN α-2b (OR 1.727 (0.72-4.13), P=0.22).

Multivariable analysis:

For composite response at week 24 post-treatment (n=29 events), the analysis included 6 predictors - age, gender, genotype (C versus B), baseline ALT level, HBV DNA (baseline) and treatment. i.e. events/covariate 4.8. The results were:

- Genotype C versus genotype B: OR 0.189 (95%CI 0.078 to 0.457); 16/60 (32%) for genotype B
- Age >25 years versus ≤25 years: OR 0.385 (95%CI 0.161 to 0.921)
- PEG interferon versus IFN: OR 1.727 (95%CI 0.721 to 4.137)
- Gender – male versus female: OR 0.593 (95%CI 0.220 to 1.597)
- Baseline ALT level ≥3.4 versus <3.4 ULN: OR 1.226 (95%CI 0.514 to 2.923)
- Baseline HBV DNA level ≥ 8.1 log10 copies/ml versus <8.1 log10 copies/ml : OR 0.527 (95%CI 0.217 to 1.280)

Thus, although the analysis included treatment, this was not significant – this may have been because there were relatively few events

Authors' conclusion: Results of the multivariate analysis revealed that HBV genotype B was independent factor associated with sustained combined response.

E.5.2 Patients treated with lamivudine

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Akuta 2003A. The influence of hepatitis B virus genotype on the	Follow up study	n= 213 .	Patients positive for hepatitis B surface antigen (HBsAg) received lamivudine monotherapy (100 mg) for more than 1 year. Inclusion: AST and ALT levels were abnormal before the commencement of the treatment, liver biopsies have been performed during the evaluation process before the onset of	Genotype A versus B versus C No multivariable analysis	Lamivudien treatment ranged between the three HBV genotypes	Lamivudine resistance (end of treatment)	None reported .

development of lamivuidine resistance during long-term treatment. Journal of Hepatology 38:315-321.			clinical disease and another biopsy was performed after symptoms had subsided; both confirming the presence of chronic hepatitis without decompensated cirrhosis and HCC. Setting: Japan Exclusion criteria: decompensated liver disease, and co-infection with hepatitis A, C or D virus, TT- virus, cytomegalovirus, Epstein-Barr, herpes simplex virus, and HIV, lifetime cumulative alcohol intake<500 kgr, no history of other liver diseases, such as autoimmune hepatitis, alcoholic liver disease, or metabolic disease. Baseline characteristics: Lamivudine resistance was not detected in any of the pretreatment serum samples from patients infected with HBV genotype A, B and C.	reported			

Characteristic	Genotype A (n=8)	Genotype B (n=20)	Genotype C (n=185)
Male: female	8:0	19:0	150:35
Age (yr) Median (range)	44 (25-49)	50 (24-66)	44 (22-71)
HBeAg positive	5 (62.5%)	3 (15%)	100 (54.1%
HBV DNA (Meq/ml) Median (range)	120 (<0.7-3800<)	8.4 (<0.7-3800<)	13.0 (<0.7-3800<)
Cirrhosis- no (%)	1 (12.5%)	2 (10%)	26 (14.1%)
Total bilirubin (mg/dl) Median (range)	0.5 (0.3-7.4)	0.7 (0.4-10.5)	0.8 (0.2-16
ALT (IU/ml) Median (range)	63 (27-2928)	93 (16-1404)	110 (16-22

			Albumin (g/dl) Median (range)	3.9 (3.1-4.5)	4.1 (3.4-4.5)	3.9 (2.6-4.8			

Results:

Both HBeAg positive and negative	Genotype A	Genotype B	Genotype C
Lamivudine resistance at the end of 1 year	12.5%	0	14.3%
Lamivudine resistance at the end of 2 years	27.1%	16.9%	27.3%
Lamivudine resistance at the end of 3 years	27.1%	16.9%	31.9%

HBeAg positive	Genotype B	Genotype C
Lamivudine resistance at the end of 1 year	0	18.8%
Lamivudine resistance at the end of 2 years	0	39.9%
Lamivudine resistance at the end of 3 years	16.9%	39.9%

Both HBeAg positive and negative	Genotype B	Genotype C
Lamivudine resistance at the end of 1 year	0	9.4%
Lamivudine resistance at the end of 2 years	0	13.8%
Lamivudine resistance at the end of 3 years	19.1%	26.1%

Authors' conclusion: Results suggested that lamivudine resistance in HBV does not seem to depend on the genotype. Lamivudine resistance according to HBeAg state might be different between HBV/B and HBV/C.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Yuen 2004. Long-term Follow-Up Study of Chinese Patients with YMDD Mutations; Significance of Hepatitis B Virus Genotypes and Characteristics of Biochemical Flares. Journal of Clinical Microbiology 2004: 3932-3936.		n= 154 .	Patients with HBeAg-positive chronic hepatitis B on long term lamivudine (participated in three trials NUCB2009, NUCB3018, NUCB4003). Inclusion: patients> =16 years old, positive for hepatitis B surface antigen (HBsAg) for at least 6 months, positive for HBeAg, had an HBV DNA level of >0.7x106 copies/ml, had ALT levels between 1.3 and 10 times the upper limit of the normal range. Exclusion criteria: none mentioned Baseline characteristics	Genotype B versus C (numbers were too small for the genotypes A, D to allow analysis) Cox regression analysis was reported, including genotype (B versus C), HBV DNA levels, ALT levels on presentation (n=43 events). Only p-values reported (0.95 for Genotype B versus C)	Ranged in the study.	1) Virological breakthrough with YMDD mutations (resistance) defined as the reappearance of HBV DNA for at least two consecutive follow-ups and the presence of YMDD mutations. 2) Biochemical flares in patients with YMDD mutations defined as increases in ALT levels>2 times the ULN from the normal ALT level in the preceding	The trials were sponsored by GlaxoSmithKline Research Laboratories.

Characteristic	All patients (n=154)	Patients with virological breatkthrough and YMDD mutations(n=43)
Male: female	117:41	30:13
Age (yr) Median (range)	31.8 (16.1-54.4)	32.4 (16.3-47.3)
ALT-U/litre Median (range)	56 (9-838)	56 (9-269)
HBV DNA-106	1,786 (11-20000)	1.222 (15-11000)

			copies/ml Median (range)				follow up.	
			Median follow up in months (range)		51.7 (28.7-71.5)			
			Genotypes -B -C	 39 (25%) 114				

Results:

	Genotype B	Genotype C	P value
Virological breakthrough with YMDD mutations (n=43)*	11/39	32/114	0.95
Biochemical flares (n=43) Median (range)	481 (88-854)	417 (71-1906)	0.78

*the authors also reported the results of a cox regression analysis by including the variables of HBV genotypes, HBV DNA, ALT levels on presentation and there was still no significant difference in the cumulative risk of virological breakthroughs with YMDD mutations between patients with genotypes B and C (P =0.95)

Authors' conclusion: the chances of YMDD mutations with virological breakthroughs and biochemical flares were similar in patients with genotypes B and C

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Chan 2003. Hepatitis B virus genotype has no impact on hepatitis B e antigen	Follow up study	n= 35 .	Patients with HBeAg-positive chronic hepatitis B who received lamivudine 100 mg daily for 12 (10-18) months. Incluson: positive for hepatitis B surface antigen (HBsAg) for at least 6 months, were negative for antibodies to HBsAg and positive for HBeAg, had an HBV DNA >1,000,000 copies per millilitre.	Genotype B versus C. HBV genotyping was performed by	15 months (range 6-34) months after lamivudine cessation.	HBeAg seroconversion at 6 months follow up defined as loss of HBeAg,	None mentioned.

seroconversion after lamivudine treatment			Setting: Prince of Wales Hospital, Hong Kong. Exclusion criteria: evidence of liver cirrhosis complications, hepatocellular carcinoma or co-infection with hepatitis C or HIV virus. Baseline characteristics Characteristic / Lamivudine (n=35) Male sex- no (%) / 25 (71%) Age (yr) Median (range) / 38 (22-47) Initial ALT (IU/ml) Median (range) / 135 (36-1122) Follow up months / 27 (18-46) Genotype -B / 14 (40%) -C / 21 (69%)	restriction fragment length polymorphism Adjusted logistic regression analysis reported, but only 4 events		appearance of antibodies to HBeAg and normalization of ALT at the end of anti-viral treatment and the response sustained for at least 6 months after cessation of treatment until the last follow up.	

Results:

	Genotype B	Genotype C	Unadjusted analysis (P value)	Adjusted analysis for age, gender, initial ALT levels and follow up duration (P value)
HBeAg seroconversion (n=35)	2/14	2/21	1.00	0.51

Authors' conclusion: HBeAg seroconversion after treatment by lamivudine was not influenced by the HBV genotype.

Reference	Study	Number of	Patient characteristics	Comparison of	Length of	Outcome	Source

<table>
<tr><th></th><th>type</th><th>patients</th><th></th><th>genotypes</th><th>follow-up</th><th>measures</th><th>of funding</th></tr>
<tr><td>Yuen 2003. Hepatitis B Genotypes in Chronic Hepatitis B and Lamivudine Therapy</td><td></td><td>n= 82

.</td><td>Patients with chronic hepatitis B with no further information on the inclusion criteria.

Setting: Hong Kong
Exclusion criteria: no information

Baseline characteristics:
<table><tr><td>Characteristic</td><td>Genotype B (n=21)</td><td>Genotype C (n=61)</td></tr><tr><td>Male sex- no (%)</td><td>15 (71%)</td><td>47(77%)</td></tr><tr><td>Age (yr) Median (range)</td><td>23.4 (16-42.6)</td><td>31.3 (16.4-48</td></tr><tr><td>Initial ALT (IU/ml) Median (range)</td><td>36 (11-398)</td><td>60 (14-506)</td></tr><tr><td>HBV DNA, x 106 copies/ml Median (range)</td><td>2,310 (5.8-48,400)</td><td>1,010 (1.8-528,000</td></tr><tr><td>Follow up period, months Median (range)</td><td>33 (26.3-66.2)</td><td>38.9 (25.4-60</td></tr></table></td><td>Genotype versus

(numbers were too small for the genotypes A, D to allow analysis)
No multivariable analysis</td><td>Week 48 (end of treatment)</td><td>1) ALT normalization
2) HBeAg seroconversion
3) YMDD mutations</td><td>Not mentioned.</td></tr>
<tr><td colspan="8">Results:<table><tr><td></td><td>Genotype B</td><td>Genotype C</td><td>P value</td></tr><tr><td>ALT normalization at 24 and 52 weeks of lamivudine treatment*</td><td>7/8</td><td>27/37</td><td>0.66</td></tr><tr><td>HBeAg seroconversion at 1 year after lamivudine</td><td>2/21</td><td>7/61</td><td>1.0</td></tr></table></td></tr>
</table>

treatment			
YMDD mutations at 1 year after lamivudine treatment	3/21	12/61	0.75

*8 patients with Genotype B and 37 patients with Genotype C had elevated ALT at baseline.

Authors' conclusion: there was no influence of HBV genotypes on the development of long-term complications and lamivudine therapy in Hong-Kong.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Tseng 2008. A higher alanine aminotransferase level correlates with earlier hepatitis B antigen seroconversion in lamivudine-treated chronic hepatitis B patients. Liver Internation	Retrospective analysis	n= 253, but 104 selected for analysis (available data) .	Patients with HBeAg-positive chronic hepatitis B and positive for hepatitis B surface antigen (HBsAg) for at least 6 months who had pretherapy serum ALT level over five times ULN. Patients received lamivudine for 12-18 months. Setting: Taiwan. Exclusion criteria: evidence of autoimmune liver disease or inheritable disorders such as haemochromatosis or Wilson's disease and a history of alcoholism and co-infection with hepatitis C or D virus or HIV virus. Baseline characteristics Characteristic: All sample (N=253) Sex (female/male): 64 (25.3%)/189 (74.7%) Age (yr) [mean±SD]: 36.2 ±11.0 Pretherapy ALT level (U/L) [mean±SD]: 525.4±346.8 Log HBV DNA (copies/ml): 7.45 ±1.87	Genotype B versus C Multivariable analysis of HBeAg seroconversion 6 months post-therapy) (n=29) reported but few details or results given	Week 48 (end of treatment) (n=and 6 months off therapy	HBeAg seroconversion at the end of lamivudine treatment and at 6 months follow up.	

al: 1478-3223.			[mean±SD]				
			Liver cirrhosis (no/yes)	244 (96.4%)/9 (3.6%)			
			Treatment duration (months) [mean±SD]	16.1 ±2.9			
			Previous lamivudine use (no/yes)	156 (61.7%)/97 (38.3%)			
			Duration of previous use of lamivudine (months) [median (range)]	8.07 (2.57-15.43)			
			HBV Genotype (B/C) (n=104)	73 (70.2%)/ 31 (29.8%)			
			Detectable lamivudine-resistant strains (no/yes) (n=104)	99 (95.2%)/ 5 (4.8%)			

Results:

	Genotype B	Genotype C
HBeAg seroconversion (at the end of treatment) (n=39)	29/73	10/31
HBeAg seroconversion (at 6 months follow up) (n=29)	21/73	8/31

Multivariable analysis for 6 months post treatment results for HBeAg seroconversion (few details) (n=29): authors reported that there were “no significant differences” for the following: age, gender, pre-therapy ALT levels, treatment duration, additional therapy after HBeAg seroconversion, viral load and genotypes B versus C; previous lamivudine usage was stated as “tended to be associated with relapse (p=0.062). This suggests 8 covariates, i.e. ratio of events/covariate = 3.6

Authors’ conclusion: No significant difference was found in terms of pretherapy serum ALT values, viral load and genotypes between seroconverters and non seroconverters.

Reference	Study	Number of	Patient characteristics	Comparison	Length of	Outcome	Source

	type	patients		of genotypes	follow-up	measures	of funding
Inoue 2011. Four-year study of lamivudine and adefovir combination therapy in lamivudine resistant hepatitis B patients: influence of hepatitis B virus genotype and resistance mutation pattern. Journal of Viral Hepatitis 18: 206-215.	Follow up study.	n= 28 .	Patients with chronic hepatitis B who were treated with lamivudine and adefovir for more than 6 months. All patients developed virological breakthrough (>1 log copies/ml increase in the HBV DNA) and adefovir was added. Setting: Japan. Exclusion criteria: co-infection with hepatitis C nor had a history of other liver diseases. Baseline characteristics	Genotype B versus C	Median 47 months (range 9-75)	1) undetectable HBV DNA<2.6 log copies/ml 2) ALT normalization	By Grant-in-Aid for Young Scientists (B) from Ministry of Education, Culture, Sports, Science, and Technology of Japan and by grants from Ministry of Health, Labor and Welfare of Japan.

Characteristic	Genotype B (n=7)	Genotype C (n=20)
Male sex- no (%)	5 (71.4%)	14 (70%)
Age (yr) [median (range)]	51 (18-70)	53.5 (35-68)
Patients with cirrhosis, n (%)	1 (14.3%)	7 (35%)
Patients with HCC, n (%)	0	7 (35%)
HBeAg positive, n (%)	3 (42.9%)	13 (65%)
HBV DNA-log copies/ml [median (range)]	7.2 (5.3->7.6)	7.6 (4.3->7.6
ALT levels, IU/L [median (range)]	314 (47-760)	78.5 (29-102

Results:

	Genotype B	Genotype C
Early virological response (HBV DNA <2.6 log copies/ml at 6	5/7	5/20

months)		

The authors also reported that the cumulative probability of undetectable HBV DNA was significantly higher in genotype B than in genotype C (P=0.0496) whereas there was no significant difference in that of ALT normalization.

Authors' conclusion: none related to genotype.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Hsieh 2009. Hepatitis B virus genotype B has an earlier emergence of lamivudine resistance than Genotype C. Antiviral Therapy 14; 1157-1163.	Retrospective analysis	N=40	Patients with chronic hepatitis B who developed lamivudine resistance during lamivudine monotherapy (100mg daily) were retrospectively screened and consecutively enrolled from the gastroenterology clinics. Among them, 11 patients received interferon based therapy prior to enrollment and the rest were naïve to nucleoside/nucleotide treatment. Inclusion: positive for HbsAg for at least 6 months before enrollment and negative for antibodies against hepatitis C virus, D and HIV infection. Setting: National Taiwan University Hospital Baseline characteristics Characteristic / Genotype B (n=24) / Genotype C (n=16) Male/female / 21/3 / 14/2 Age (yr) / 39.2±2.6 / 35±3.3	Genotype B versus C Multivariable linear regression on time to resistance – appears to have been analysed on the continuous variable time, despite Kaplan Meier plot	No	Time to lamivudine resistance (3TC-R HBV). Early emergence of lamivudine resistance was define as a detectable mutation strain within 12 months of treatment. The detection of lamivudine resistant strains was performed whenevever a biochemical breakthrough occurred (increase in serum ALT level above the upper limit of normal	By grants from the National Taiwan University Hospital, Department of Health and the National Science Council, Executive Yuan, Taiwan, National Helath Research Institutes, and Liver Disease Prevention

			mean±SD					after achieving normalization).	and Treatment Research Foundation.
			ALT, IU/L	399.3±74.5	288.5±99.5				
			HBeAg (positive:negative), n(%)	14 (58.3%)/10 (41.7%)	12 (75%)/4 (25%)				
			HBV DNA log10 IU/ml	8.04±7.56	7.86±7.48				
			Time to first resistant strain, months (range)	17.2±2.2 (7-47)	23.3±2.4 (10-48)				
			HBeAg (positive/negative), n(%)	12 (50%)/12 (50%)	11 (69%)/5 (41%)				

Results:

Genotype B patients tended to have shorter interval to develop lamivudine resistance than Genotype C patients (17.2 versus 23.3 months) (P=0.06)

13/24 in genotype B group and 2/16 in the genotype C group experienced early emergence of lamivudine resistance. By multivariable linear regression on time to resistance analysis (including age, gender, genotype, pretreatment HBV DNA, HBeAg status and ALT levels), genotype B was one of the independent factors associated with earlier detection of lamivudine resistance (occurred within the first 12 months of treatment) (P=0.04)

In terms of early lamivudine resistance, genotype B was significantly associated with development of lamivudine resistance within the first 12 months (P=0.004) compared to Genotype C with an odds ratio (OR) of 8.27.It is unclear whether this was a multivariable analysis.

Lamivudine resistance pattern (YIDD or YVDD) were not associated with HBV genotype.

Authors' conclusion: Compared with Genotype C, genotype B appears to have an earlier biochemical resistance to lamivudine.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Suzuki	Cohort	n= 234	Patients positive for hepatitis B surface antigen (HBsAg) and	Genotype B	Week 48	HBeAg	None

2003. Efficacy of Lamivudine Therapy and Factors associated with Emergence of Resistance in Chronic Hepatitis B Virus Infection in Japan. Intervirology 46: 182-189.	study	.	HBV DNA over 3 months prior to commencement of lamivudine therapy and were negative for hepatitis C serological markers. All patients had an elevated serum ALT for 3 months before the commencement of therapy. None of the patients had hepatocellular carcinoma at the start of therapy. Lamivudine was administered orally at 100, 150 or 300 mg/day. 47% of patients were HBeAg positive Setting: Baseline characteristics Characteristic / N=234 Femakes/males / 46/188 Age (yr) / 44 (22-70) Family history of liver disease / 147 (64.5%) Cirrhosis / 31 (13.2%) Median duration of treatment, months (range) / 25 (12-83) ALT, IU/litre / 110 (16-2,928) Serum HBV DNA (Meq/ml) / 16.5 (0.5-4,000) HBeAg positive / 111 (47.4%) Per genotypes -A / 6/8 -B / 4/21 -C / 100/203 -other / 1/2 Genotypes -A / 8 -B / 21 -C / 203	versus C (numbers were too small for the HBeAg positive group allow analysis) Multivariable Cox regression analysis was conducted across both HBeAg positive and HBeAg negative groups for the emergence of mutation of the YMDD motif. All factors that were at least marginally associated (p<0.1) with emergence were tested in the multivariable model	(end of treatment)	seroconversion was defined as undetectable HBeAg and detectable anti-Hbe. Emergence of lamivudine resistance (mutation of the YMDD motif) (n=60 events)	mentioned.

			-other	2			

Results:

	Genotype A (n=8)	Genotype B (n=21)	Genotype C (n=203)
ALT normalization during the first year of lamivudine therapy			
HBeAg positive (n=4)	5/8	4/4	82/98
HBeAg negative (n=17)		17/17	89/102
ALT normalization during the second year of lamivudine therapy			
HBeAg positive (n=4)	4/5	2/2	44/52
HBeAg negative (n=4)		10/11	40/50
Undetectable HBV DNA (<0.7 X 106 genomics equivalents/ml) during the first year of lamivudine therapy			
HBeAg positive (n=4)	6/8	3/3	78/95
HBeAg negative (n=4)		14/15	95/101
Undetectable HBV DNA (<0.7 X 106 genomics equivalents/ml) during the second year of lamivudine therapy			
HBeAg positive (n=4)	2/5	2/2	39/51
HBeAg negative (n=4)		10/11	46/49

Multivariable analysis:

For emergence of resistance during treatment, (n=60 events), the analysis included 3 predictors - HBV DNA level, HBeAg (positive versus negative) and stage of hepatitis.

- Genotype A, B and C were not statistically significant on univariate analyses (no details given) and were not entered into the multivariable model; however, genotype C dominated the distribution of genotypes (203/232 – 96%)

A second multivariable analysis in patients who were genotype C only (n=52 events) with the same covariates showed

- HBeAg positive versus negative: HR 2.06 (95%CI 1.06 to 3.98); p=0.0327
- HBV DNA level was also significant

Authors' conclusion: Rates of ALT normalization and non-detection of HBV DNA were higher among patients with genotype B than genotype C disease.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Chien 2003. Determinants for Sustained HBeAg Response to Lamivudine Therapy. Hepatology 38: 1267-1273.	Cohort study	n= 82 .	Patients with HBeAg-positive chronic hepatitis B and HBV DNA for 6 months. They were treated with lamivudine for a mean period of 16 months (range 3-55) and achieved complete response. Setting: Exclusion criteria: co-infection with hepatitis C or D virus or IV virus. Previous treatment fro chronic hepatitis B was permitted, but not within the 6 months before the study. Baseline characteristics Characteristic / Genotype B (n=62; 76% of all) / Genotype C (n=20) Male/female: 47/15 / 16/4 Age (yr) mean±SD: 30.4±9.0 / 34.9±10.3 ALT-U/litre mean±SD: 474.3±457.0 / 568.7±540.5 >=180 U/L: 43 (69%) / 18 (90%) HBV DNA-log copies/ml mean±SD: 1,478.8±2,575.5 / 1,068.8±2,130.4 Fibrosis scores: 1.6 ±1.2 / 2.4 ±1.4	Genotype B versus C Statistical analysis: for the outcome sustained response to treatment after 12 months (43/82), multivariable logistic regression analysis was conducted. Variables significant on univariate analysis (p<0.10) were included in the analysis, with stepwise elimination. Patients with missing values were not included (number	All patients were followed up for at least 12 months after end of therapy.	Complete response was defined as normalization of serum ALT level, loss of serum HBV DNA by hybrid capture assay and seroconversion of HBeAg to its antibody (anti-Hbe). Patients with complete response sustained for 12 months after the end of lamivudine therapy were classified as sustained responders.	None mentioned.

			Precore stop codon mutation	14/36	2/7	not stated)		
			Core promoter mutation	12/51	10/18			

Results:

	Genotype B	Genotype C	OR (95% CI)	P value
Sustained HBeAg response	38/62	5/20	5.922 (1.611-21.768)	0.009

Multivariable analysis:

For sustained response during treatment, (n=43 events), the analysis included 5 predictors – age, ALT level, genotype B versus C, additional treatment time after seroconversion and total treatment time; i.e ratio events/covariates = 8.6.

- Genotype B versus C: OR 5.922 (95%CI 1.611 to 21.768); p=0.007
- Age: OR 0.943 (95%CI 0.891 to 0.97); p=0.040 (assumed per year)
- Additional treatment: OR 1.097 (95%CI 1.028 to 1.171); p=0.005

Authors' conclusion: Genotype was one of the independent factors to predict sustained HBeAg response; patients with genotype B have higher sustained response to lamivudine treatment.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Kobayashi 2006. Response to Long-Term Lamivudine Treatment	Cohort study	n= 502 .	Patients persistently infected with HBV and diagnosed with chronic liver disease received oral lamivudine 100 mg/day for longer than 1 year. Chronic hepatitis (84.9%) was diagnosed by liver biopsies performed under laparoscopy, and cirrhosis (14.5%) by liver biopsy and/or ultrasonographic images plus laparoscopic findings. They were given lamivudine for a median of 6.9 years (range 1-10.2 years). 264/502 (53%) were HBeAg positive; 3%, 8% and 89% were genotypes A, B and C	Genotype A versus B versus C Statistical analysis: for the outcome emergence of resistance (YMDD	For a median of 6.9 years (0.1-31.2).	Lamivudine resistance (emergence of YMDD mutants); breakthrough hepatitis (unclear how	None mentioned.

in Patients Infected with Hepatitis Virus Genotypes A, B and C. Journal of Medical Virology 78:1276-1283.			respectively. Baseline characteristics (table below) *patients with genotype A were significantly younger, had higher levels of HBV DNA and HBeAg positive more frequently than those with genotype B or C.	mutants) (208/502)), and for development of breakthrough hepatitis (unclear number of events, but about 176), multivariable Cox proportional hazard regression analysis was conducted. Variables significant on univariate analysis (p<0.05) were included in the analysis, with stepwise elimination		defined)	

Characteristic	Genotype A (n=15)	Genotype B (n=38)	Genotype (n=449)
Male sex- no (%)	14 (93%)	34 (91%)	359 (80%
Age (yr)	37 (24-49)	47 (24-67)	44 (18-73
Treatment duration (years)	2.7 (1.2-5.2)	2.3 (1.0-5.7)	3.6 (1.0-9
Chronic hepatitis	13 (87%)	33 (87%)	383 (85%
Cirrhosis	2 (13%)	5 (13%)	66 (15%)
HBV DNA (LGE/ml)	8.6 (6.1-8.7)	6.5 (<3.7-8.7)	6.5 (<3.7-
HBeAg status positive	11 (73%)	8 (21%)	245 (56%

Results:

	Genotype A	Genotype B	Genotype C	P value
Lamivudine resistance during follow up				
HBeAg positive	9/11 (82%)	2/8 (25%)	117/245 (48%)	0.037
HBeAg negative	3/4 (75%)	9/30 (30%)	68/204 (33%)	0.003
Proportion with given genotype	15/502 (3%)	38/502 (8%)	449/502 (89%)	

Multivariable analysis:

For emergence of resistance during treatment, (n=208 events), the predictors included in the analysis was unclear. Significant predictors were:

- Genotype A versus B: HR 2.78 (95%CI 1.08 to 7.12); p=0.034; it is noted that the proportion of both genotypes A and B are very low (3% and 8%)
- Genotype C versus B: HR 1.23 (95%CI 0.62 to 2.42); p=0.56; it is noted that the proportion of genotype B is low 8%
- HBeAg positive versus negative: HR 2.11 (95%CI 1.53 to 2.92); p<0.001

For the development of breakthrough hepatitis during treatment, (n=about 176 events), the predictors included in the analysis was unclear. Significant predictors were:

- ALT levels <500 versus ≥500 U/l: HR 2.56 (95%CI 1.82 to 5.56); p=0.018
- Cirrhosis versus chronic hepatitis: HR 1.92 (95%CI 1.24 to 2.97); p=0.004
- HBeAg positive versus negative: HR 2.11 (95%CI 1.40 to 3.16); p<0.001
- HBV DNA >8 log10 copies/ml: HR 1,57 (95%CI 1.04 to 2.36); p=0.03
- There was no significant effect of genotype

Authors' conclusion: HBV genotypes help in predicting response to long-term lamivudine treatment and development of YMDD mutants in patients with chronic hepatitis B.

E.5.3 Patients receiving adefovir treatment

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Zeng 2008. Hepatitis B Virus Genotype-Associated Variability in Antiviral Response to Adefovir	Retrospective analysis of prospective RCTs adefovir arms only	N=183	Patients with HBeAg-positive chronic hepatitis B who had been treated with adefovir (10mg daily) (phase III trials) for 48 weeks at the outpatient and inpatient department of the first affiliated hospital of Chongquing Medical University. Inclusion: aged between 18-70 years, HbsAg positive in serum for at least 6 months, presence of HBeAg and HBV DNA in serum and elevation of serum ALT levels at	Genotypes B versus C Statistical analysis: for the outcome initial virological response	No	-Initial virological response defined as HBV DNA levels decreased to less than 104 copies/ml after 24 weeks of adefovir therapy. -HBeAg loss (at	By a grant from the National Basic Research Program.

Dipivoxil Therapy in Chinese Han Population. Tohoku J. Exp. Med 2008: 216; 205-211.			least 2 times higher than the normal value. Exclusion criteria: chronic liver diseases other than HBV DNA had been excluded by appropriate clinical and laboratory evaluations. History of malignancy, HIV infection, liver cirrhosis on ultrasonography, evidence of decompensated liver disease, prior use of antiviral treatment or immunomodulatory agents within 6 months that could influence treatment outcomes, pregnant women. Baseline characteristics	(57/183), multivariable regression analysis was conducted. Variables significant on univariate analysis (p<0.05) were included in the analysis.		week 48-end of treatment) -HBeAg seroconversion(at week 48-end of treatment) -ALT normalization (at week 48-end of treatment)	

Characteristic	Genotype B (n=98)	Genotype C (n=75)	P v
Male/female	78/20	61/14	0.4
Age (yr) mean±SD	31.6±8.6	33.1±9.8	0.2
Mean ALT (U/L)	166.1±105.2	171±92.3	0.0
Mean serum HBV DNA (log10 copies/ml)	7.7±1.5	7.9±1.7	0.3

Results:

	Genotype B (n=98)	Genotype C (n=75)	P value
Early virological response (HBV DNA <104 copies/ml after 24 weeks of adefovir therapy)	34 (34.7%)	23 (30.7%)	0.172
HBeAg loss (end of 48 weeks treatment)	31 (31.6%)	23 (28.8%)	0.152
HBeAg seroconversion (end of 48	22 (22.4%)	15 (18.8%)	0.376

weeks treatment)			
ALT normalization (end of 48 weeks treatment)	81 (82.7%)	60 (80%)	0.226

Multivariable analysis:

For initial virological response after 24 weeks, (n=57 events), the analysis included 3 predictors – age, ALT levels and HBV DNA level; i.e. ratio of events/covariates of 19

- Genotype B versus C was not statistically significant on univariate analyses and was not entered into the multivariable model
- Age: OR 1.06 (95%CI 0.92 to 1.37); p=0.038 (as reported by authors; CI incorrect?)
- Elevated pre-treatment ALT level: OR 0.097 (95%CI 0.013 to 0.710); p=0.017
- Decrease in pre-treatment HBV DNA level: OR 1.11(95%CI 0.97 to 1.25); p=0.031(as reported by authors; CI incorrect?)

Authors' conclusion: There were no statistically significant differences between genotypes B and C in terms of HBeAg loss, HBeAg seroconversion and ALT normalization.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Westland 2003. Hepatitis B Virus Genotypes and Virological Response in 694 Patients in Phase III Studies of Adefovir Dipivoxi. Gastroenterology 2003; 125: 107-116.	Retrospective analysis	N= 694.	Patients with chronic hepatitis B who took part in 1 of 2 randomized double blinded placebo controlled phase III trial of adefovir dipivoxil (GS-98-437 and GS-98-438and who received adefovir. Entry criteria and baseline characteristics Characteristic / GS-98-437 / GS-98-438 Entry criteria -HBeAg status: Positive / Negative -HBV DNA (log10copies/ml): >=6 / >=5 -ALT (x ULN): 1.2-10.0 / 1.5-15.0	Genotypes A,B,C,D,E,F,G Statistical analysis: Multivariable analysis of variance analyses were conducted, adjusting for baseline ALT and serum HBV DNA levels to determine the effect of different genotypes (n=269 events); few details	No	Antiviral response defined as reduction in serum HBV DNA (log10 copies/ml)	None mentioned.

(min-max)		
Baseline characteristics		
ITT patients (n)	511	184
Male/female	74%/26%	83%/17%
Genotypes -A -B -C -D -E -F -G	 29% 20% 36% 11% <1% 1% 2%	 6% 17% 13% 62% 2% <1% 0%
Race -Asian -Caucasian -Black -Other	 59% 36% 3% 1%	 30% 66% 3% 0%
Mean age (SD)	35 ±11.3	46 ±10
Mean ALT (x ULN) ±SD	3.3 ±3.2	3.5 ±3.6
Mean HBV DNA (log10 copies/ml) ±SD	8.2 ±0.9	6.9 ±0.9

Results:

For HBeAg positive patients, analysis of baseline serum HBV DNA levels revealed significant differences between genotypes (P<0.001); within the genotypes (A-D), genotype C was associated with significantly lower levels of serum HBV DNA than genotypes A, B and D (P<0.001). Genotype B was associated with signficantly lower levels of serum HBV DNA than genotype A (P<0.01).

For HBeAg negative patients, there were significant differences in baseline serum HBV DNA levels between the genotypes (P=0.001); genotype D patients had higher mean levels of serum HBV DNA than genotypes A,B, C (P<0.01). No other differences were significant.

	Genotype A (n=43)	Genotype B (n=52)	Genotype C (n=71)	Genotype D (n=96)

Reduction in HBV DNA (log copies/ml at 6 months) Mean (SD)	-3.58 (1.95)	-3.42 (1.33)	-3.65 (1.35)	-3.68 (1.28)

Multivariable analysis:

For virological response after 48 weeks, (n=269 events), the analysis included 3 predictors – age, ALT levels and HBV DNA level plus genotypes A to G; i.e. ratio of events/covariates > 10. No odds ratios were reported, but the authors stated that there were no significant differences in antiviral response among the genotypes (P=0.931). The analysis did not appear to allow for HBeAg seropositivity, but stated that there was equal antiviral efficacy in patients who were HBeAg positive and negative (p=0.503)

Authors' conclusion: Forty-eight weeks of adefovir therapy resulted in significant decreases in serum HBV DNA levels in patients regardless of HBV genotype, HBeAg status or race.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Buti 2007. Viral genotype and baseline load predict the response to adefovir treatment in lamivudine-resistant chronic hepatitis B patients. Journal of Hepatology 47: 366-372.	Retrospective analysis (collected from consecutive patients files and virological records)	N=54	HBeAg-positive and negative patients with chronic hepatitis B and with lamivudine resistance confirmed by detection of mutations in the YMDD motif of the RNA dependent DNA polymerase gene of the virus (genotypic resistance), elevated serum HBV DNA levels (at least 4 logs and/or more than 1 log elevation from the LAM on treatment nadir) and/or elevated serum HBV DNA levels (at least 4 logs and or more than 1 log elevation from the LAM on treatment nadir) and/or elevated ALT levels (>40IU/L). Patients were treated with adefovir either as monotherapy (10mg/day) or in combination with ongoing lamivudine (100 mg/day).	Genotype A versus D Multivariable Cox proportional hazards analysis conducted using 10 fixed covariates (n=38 events for virological response). Only 6 patients had HBeAg loss. No further details given about the analyses	no	-Virological response defined as serum HBV DNA <104 copies/ml within the first 12 months of treatment as well as during the on treatment follow up period. -HBeAg loss	None mentioned.

Setting:Department of Hepatology of the Vall d'Hebron University Hospital, Barcelona.

Exclusion criteria: decompensated liver cirrhosis, hepatocellular carcinoma, liver transplant, received immunotsuppressive medication or if they had co-infections (HIV, HCV, HDV) or other concomitant liver diseases.

Baseline characteristics of the study population

Characteristic	N=54
Male sex- no (%)	44 (81.5%)
Age (yr) mean±SD	51.1±12.1
BMI	25.6±3.4
Lamivudine treatment duration (months)	32.6±22.7
ALT (IU/L)	113±67.2
HBV DNA (log10 copies/ml)	6.98±1.28
HBeAg positive (%)	25 (46.3%
Genotype A/D/other)	23/29/2
Cirrhosis	20 (37%)
Treatment group -adefovir -adefovir +lamivudine	 28 (51.8%) 26 (48.2%)

Results:

Multivariable analysis:

For virological response after 12 months, (n=38 events), the analysis included 10 predictors – age, BMI, duration of Lamividune therapy, baseline serum ALT levels and HBV DNA levels, gender, HBV genotype, HBeAg status, cirrhosis, treatment group (ADV monotherapy or ADV+Lam combination); i.e. ratio of events/covariates of 3.8

- Genotype A versus D was not statistically significant on multivariable analysis; on univariate analysis HR 0.65 (95%CI 0.33 to 1.27); p=0.20
- Gender male versus female: HR 0.20 (95%CI 0.05 to 0.76); p=0.018
- HBeAg positive versus negative: HR 0.37 (95%CI 0.14 to 0.96); p=0.040
- HBV DNA level: HR 0.65 (95%CI 0.45 to 0.95) per 1 log10 increase

For HBeAg loss, there were only 6 events, which gives <<10 events/covariate and results are therefore to be disregarded.

Authors' conclusion: Genotype D HBV infection independently predict HBeAg loss.

Reference	Study type	Number of patients	Patient characteristics	Comparison of genotypes	Length of follow-up	Outcome measures	Source of funding
Hass 2009. Rapid HBV DNA decrease (week 12) is an important prognostic factor for first-line treatment with adefovir depivoxil for chronic hepatitis B. J Gastroenterol 44: 871-877.	Retrospective analysis	N=66	Patients with chronic hepatitis B and elevated serum alanine transaminase (ALT) on at least two occasions, detectable baseline HBV DNA level (>= 2,000 UI/ml) and without decompensated liver chirrhosis as well as no prior antiviral or immunomodulatory treatment for CHB received adefovir (10mg daily) for 96 weeks. 69.7% were HBeAg negative. Baseline characteristics Characteristic: Genotype A (n=18); Genotype D (n=44); Genotyp (n=4) Gender (male %): 63.1%; 61.7%; 25% Age (yr): 44.5±11.9; 40.9±13.7; 38±2	Genotype A, D and E No multivariable analysis conducted	No	Biochemical response at the end of treatment (96 weeks)	None mentioned.

			mean±SD						
			ALT (U/L)	83±56	173±268	53±12			
			Baseline viral load (I.E/ml)	5.04x107 (±10.8 x107)	2.27x107 (±6.83 x107)	2.01x10 (±3.8 x1			
			Evidence of cirrhosis	16.6%	11.3%	25%			
			HBeAg negative	72.2%	68.2%	75%			

Results:

	Genotype A (n=18)	Genotype D (n=44)	Genotype E (n=4)	P value
Biochemical response (at the end of 96 weeks of adefovir treatment)	77.7%	47.7%	75%	0.1

Authors' conclusion: none related to genotype.

E.6 Antiviral treatment

E.6.1 Pharmacological therapies

E.6.1.1 Monotherapies for HBeAg positive treatment-naïve adults with CHB infection

Adefovir vs placebo

Reference	Study type	Number of	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source

		patients						**of funding**
Marcellin 2003	RCT Central randomisation. Stratified according to seven geographic regions. Permuted blocks (with a block size of 6) were used in each stratum. Double blind.	n=338 (10mg vs placebo arms only)	Patients with chronic hepatitis B who were positive for hepatitis B e antigen (HBeAg +ve) Setting: Multi centre (78 centres in North America, Europe, Australia and South-East Asia) Inclusion: Male and female patients 16 to 65 years of age who had hepatitis B e antigen-positive chronic hepatitis B and compensated liver disease were eligible for the study. Chronic hepatitis B was defined by the presence of serum hepatitis B surface antigen for at least 6 months, a serum HBV DNA level of at least 1 million copies per millilitre, and a serum alanine aminotransferase level that was 1.2 to 10 times the upper limit of the normal range. Patients were required to have a prothrombin time that was no more than one second above the normal range, a serum albumin level of at least3g per decilitre, a total bilirubin level of no more than 2.5 mg per decilitre, a serum creatinine level of no more than 1.5 mg per decilitre, and an adequate blood count. Women of childbearing potential were eligible if they had a negative pregnancy test and were using effective contraception. Exclusion: Co-existing serious medical or psychiatric illness; immune globulin, interferon, or other immune- or cytokine based therapies with possible activity against HBV disease within 6 months before screening; organ or bone marrow	Adefovir dipivoxil 10 mg for 48 weeks (n=172 randomised; 171 baseline data; 168 had final histological data) Third arm: Adefovir dipivoxil 30 mg for 48 weeks (n=173 randomised; 173 baseline data; 165 final histological data) – not statndard dose so not data extracted	Placebo for 48 weeks (n=170 randomised; 167 baseline data; 161 final histological data)	Week 48 (end of treatment)	Log reduction of serum HBV DNA levels. Proportion of patients with undetectable levels of HBV DNA (lower limit of detection 400 copies/mL) change in ALT and % patients with ALT normalisation % patients with loss or seroconversion of HBeAg % patients with histologic improvement (defined as a reduction of at least two points in the Knodell	Gilead sciences

transplantation; recent treatment with systemic corticosteroids, immunosuppressants, or chemotherapeutic agents ; a serum alpha-fetoprotein level of at least 50ng per millilitre; evidence of a hepatic mass; liver disease that was not due to hepatitis B; prior therapy for more than 12 weeks with a nucleoside or nucleotide analogue with activity against HBV; and seropositivity for HIV or hepatitis C or D virus.

Baseline characteristics

Characteristic	Placebo (n=167)	Adefovir 10 mg (n=171)
Age-yr (mean ±SD)	37±11.8	34±11.2
Male sex- n (%)	119 (71)	130 (76)
Alanine aminotransferase (mean ±SD) U/litre	139±131	139±154
HBV DNA-log copies/ml (mean ±SD)	8.12±0.89	8.25±0.90
Total Knodell score (mean ±SD)	9.65±3.45	9.01±3.33
Knodell necroinflammatory score (mean ±SD)	7.83±2.89	7.37±2.75
Knodell fibrosis score (mean	1.83±1.12	1.64±1.09

necroinflammatory score with no concurrent worsening of the Knodell necrosis score 48 weeks after baseline)

			±SD)								

Effect size (week 48)*

	Adefovir 10 mg n=171	Placebo n=167
Change in serum HBV DNA –log copies/ml mean±SD	-3.57±1.64 p<0.001 vs. placebo	-0.98±1.32
Patients with undetectable HBV DNA (<400 copies/mL) – n (%)	36/171 (21%)	0 (0%)
HBeAg seroconversion**- n /total n (%).	20/171 (12), p<0.049 vs. placebo	9/161 (6)
HBeAg loss- n/total n.(%)	41/171 (24), p<0.001 vs. palcebo	17/161 (11)
Normalisation of ALT - n/total n (%)	81/168 (48), p<0.001 vs. placebo	26/164 (16)
Histologic improvement – n (%)	89/168 (53)	41/161 (25)
Resistance	0	0
Discontinuation of the study prematurely due to adverse events (%)***	2%	<1%

*the number of patients is the number with assessable liver-biopsy specimens at baseline and week 48.

**seroconversion was defined as loss of HBeAg and concurrent gain of antibody against HBeAg at 48 weeks.

***these events included increased alanine aminotransferase or aspartate aminotransferase levels, weight loss, and rash in the 10 mg group; nausea, abdominal pain, headache, Fanconi-like syndrome, amblyopia and myocardial infarction in the 30 mg group; and nausea in the placebo group.

Authors' conclusion:

In patients with HBeAg-positive chronic hepatitis B, 48 weeks of 10 mg or 30 mg of adefovir dipivoxil per day resulted in histologic liver improvement, reduced serum HBV DNA and alanine aminotransferase levels, and increased the rates of HBeAg seroconversion. The 10 mg dose has a favourable risk-benefit profile for long-term treatment. No adefovir-associated resistance mutations were identified in the HBV DNA polymerase gene.

NOTE: Treatment naïve and previously treated with IFN (24% patients; percentage in each group not stated).

Sample size calculation: the study was designed to enrol 166 patients per group, with 90% power to detect an absolute different of 20% (50% vs. 30%) between the group given 10mg of ADV and the placebo group, assuming that 25% of patients would have missing biopsy specimens that would be considered treatment failures and that 8% of patients would have missing baseline biopsy specimens, on the basis of a 2-sided type I error rate of 0.05.

The study had 79% power to detect an absolute difference of 10% (16% vs 6%) in seroconversion rate between the groups, assuming that 10% patients would have missing values (which were counted as treatment failures).

Patients with missing or unassessable data at 48 weeks were considered not to have had responses.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Tseng 2009a. HBV DNA level as an important determinant of E antigen seroconversion of CHB during adefovir dipivoxil therapy.	RCT Phase III randomised controlled trial Randomisation: centrally randomised 1:1:1 Retrospective analysis of a small subset of patients from a RCT (Marcellin, 2003)	52	HBeAg positive Inclusion: male and female, 16 to 65 years old with HBsAg for at least 6 months, HBeAg positive, serum HBV DNA ≥10^6 copies/mL, ALT levels around 1.2 to 10 times ULN Setting: Taiwan Exclusion: Coinfection with Hep C or D virus or HIV infection; prior therapy for more than 12 weeks with a nucleos(t)ide analogue; recent treatment with IFN, systemic steroid, immunosuppressants, or chemotherapeutic agents; a serum alpha-fetoprotein level of at least 50ng/ml; evidence of liver mass; and/or decompensated liver disease Baseline characteristics ADV (n=33) / Placebo (n=19) / P value Mean age (SD): 30.61 (8.33) / 33.45 (9.56) / NS Mean BMI: 23.42 / 22.33 / NS	Adefovir 10mg/day or 30mg/day* (n=33) Total duration of treatment: 1 year *two ADV groups have been pooled into a single ADV group	Placebo (n=19) Total duration of treatment: 1 year	Post treatment at 1 year	HBV DNA (<10^5 copies/ml) HBV DNA was quantified by PCR assay using Roche Amplicor HBV Monitor PCR assay with a lower limit of detection of 400 copies/mL HBeAg seroconversion (HBeAg clearance and anti-HBe development)HBsAg, HBeAg and anti-HbE were detected by using a commercial kit (Abott laboratories)	Not stated

			(SD)	(3.33)	(2.09)					
			Male/female, n	26/7	8/11	p=0.007				
			Mean serum HBV DNA (SD), log_{10} copies/ml	8.13 (0.75)	7.87 (0.80)	NS				
			Mean serum ALT (SD), ULN	3.45 (5.01)	2.92 (2.52)	NS				
			Genotype B/C, n	18/15	8/11	NS				
			Mean HAI grade (SD)	6.24 (3.45)	6.89 (3.02)	NS				
			Mean HAI fibrosis (SD)	1.55 (1.18)	1.68 (1.06)	NS				
			Cirrhosis, yes/no	2/31	1/18	NS				

Effect size

Notes: This is a retrospective analysis of a small subgroup of patients from a RCT (Marcellin 2003). Baseline factors such as HBV DNA, ALT, gender, age, etc were explored as explanatory variables using multivariate logistic regression. Factors which have been well characterised as independent determinants for the prognosis of CHB infection were treated as potential confounders. The authors report univariate and multivariate analyses predicting the endpoints of a) HBeAg seroconversion and b) HBV DNA < 10^5 copies/mL. However, as they only analysed 52 patients of the original 388 (not stated why they did not use the entire sample; **all results should be interpreted with caution due to potential bias introduced by only using 13% of the potential data**), there was no significant difference in outcome between the treatment and control groups used here (HBeAg seroconversion 21.2% adefovir and 26.3% placebo).

Factors which significantly predicted HBeAg seroconversion in multivariate analysis: baseline HBV DNA (log copies/mL): OR 0.04 (95% CI 0.01 to 0.44), p=0.010.

Factors which significantly predicted HBV DNA < 10^5 copies/mL in multivariate analysis: baseline HBV DNA (log copies/mL): OR 0.12 (0.03 to 0.50), p=0.004; treatment (yes vs. no): OR 90.03 (6.47 to 1252.38 [note very wide CI]), p=0.001

Authors' conclusion: Low pre-treatment HBV DNA level is predictive of HBeAg seroconversion in patients treated with Adefovir or placebo. Adefovir may provide additional benefits for HBeAg seroconversion in patients with pre-treatment HBV DNA levels between 10^7 and 10^8 copies/ml. Profound early HBV DNA reduction may

contribute to HBeAg seroconversion.

Lamivudine vs placebo

Reference	Study type	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Dienstag 1999	Double blinded multicentre RCT Randomisation and allocation concealment not reported.	Previously untreated HBeAg positive patients with chronic hepatitis B Inclusion: Patients over 18 years of age with detectable serum hepatitis B surface antigen (HBsAg) for at least 6 months, serum hepatitis B e antigen (HBeAg) for at least one month, and serum alanine aminotransferase levels that were 1.3 to 10 times the upper limit of the normal range for at least 3 months. Patients also had to have evidence of chronic hepatitis on liver biopsy and detectable levels of serum HBV DNA according to a hybridisation -assay (limit of detection was approximately 1.6pg per millilitre). Setting: 34 U.S. centres Exclusion: Pregnant/breastfeeding women, patients with previous antiviral treatment for hepatitis B; treatment with antiviral agents, immunomodulatory drugs, or corticosteroids within 6 months before the study began; bilirubin level >2.5mg/dL, prothrombin >3s longer than normal, albumin <3.5g/dL, history of ascities, variceal haemorrhage, hepatic encephalopathy, coninfection with hepatitis C, D or HIV, nuclear antibody titre >1:160, creatinine >1.5mg/dL, Hb <11g/dL, white cell count	Lamivudine 100 mg once daily orally for 52 weeks. (n=66) No losses to follow up.	Placebo once daily for 52 weeks (n=71) No losses to follow up.	52 weeks treatment + 16 weeks follow up	% of patients with undetectable HBV DNA (by Abbot assay-threshold not reported) HBeAg seroconversion HBeAg loss ALT normalization HBsAg loss Adverse events Primary: Histologic	Glaxo Wellcome, the Hepatitis Research Fund of Massachusetts General hospital and a Clinical Research Center grant from the National Institutes of Health.

		<3000/mm^3, neutrophils <1500/mm^3, platelets <100,000/mm^3 or the presence of confounding medical illness or other types of liver disease. Baseline characteristics *serum levels of HBV DNA were higher in the lamivudine group at baseline.				improvement (reduction of at least 2 points on the Histologic Activity Index; range 0 [normal] to 22 [most severe abnormalities]) Incidence of genotypic YMDD mutation	

Characteristic	Lamivudine (n=66)	Placebo (n=71)
Age (yr) median	40	38
Male sex (%)	86	80
White Asian Black Other/unknown	59% 24% 15% 2%	56% 17% 18% 9%
Histologic Activity Index score median (range)	10 (0-15)	11 (3-17)
Serum HBV DNA (pg/ml) median (range)*	102.2 (0.8-1753)	56.5 (0.8-653)
Serum alanine aminotransferase level (U/litre)	125 (46-401)	135 (33-592)

Effect size

Outcomes	Lamivudine group (n=66)	Placebo group (n=71)	p-value
Outcomes (end of 52 week treatment)			
% of patients with undetectable HBV DNA	28/63 (44%)	11/69 (16%)	p<0.001
HBe Ag seroconversion	11/63 (17%)	4/69 (6%)	P=0.04
Loss of serum HBeAg	21/66 (32%)	8/71 (11%)	P=0.003
Histologic improvement (no. of patients with reduction of at least 2 points in the Histologic	34/66 (52%)	16/71 (23%)	P<0.001

Activity Index)			
Normalization of ALT levels	27/66 (41%)	5/68 (7%)	p<0.001
Incidence of genotypic YMDD mutation	14/44 (32)	not tested	
Outcomes (16 week follow up)			
HBe Ag seroconversion	11/63 (17%)	6/69 (9%)	not reported
Loss of serum HBe Ag	19/66 (29%)	11/71 (15%)	not reported
Loss of serum HBsAg	1/66 (2%)	0/71 (0%)	not reported
Undetectable HBV DNA ((1.6pg/mL)	17/52 (33%)	16/53 (30%)	not reported

Authors' conclusion:

In US patients with previously untreated chronic hepatitis B, one year of lamivudine therapy had favourable effects on histologic, virologic and biochemical features of the disease and was well tolerated. HBeAg responses were usually sustained after treatment.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yao 1999, Yao 2000, Yao 2002, Yao 2004 (same patients)	Multicentre double blind-RCT for 12 weeks, then all participants in lamivudine for 104 weeks. - randomization method; unclear - blinding; unclear	N=429	Inclusion: HBeAg positive, HbsAg positive and HBV DNA positive patients in the 6 months before screening aged 16-65 years who had ALT concentrations <10 x normal ULN. Setting: China Exclusion: decompensated liver disease (bilirubin >2.5 x ULN, prothrombin time prolonged >3s, albumin < reference range, history of ascites, variceal haemorrhage and hepatic encephalopathy), coinfection with hep C, delta or HIV, use of antiviral or cytotoxic or corticosteroids or immunomodulators within the last 6 months, evidence of autoimmune or hereditary liver disease, bone marrow suppression, creatinine >1.5 x ULN, serious concurrent illness, alcoholism, drug abuse, history of hypersensitivity to nucleoside analogues, pregnant/lactating women,	Lamivudine (100mg/day) (n=322) Total duration of treatment: 12 weeks Loss to follow up/reasons: 9 (loss to follow up or personal	Placebo (n=107) Total duration of treatment: 12 weeks Loss to follow up/reasons: 2 (loss to follow up or personal	Different follow ups in Yao 2000, 2002, 2004	1) % with undetectable HBV DNA (<1.6pg/ml – the lower limit of detection measured by Genostics assay) 2)% with ALT normalisation (threshold) 3)% with HBeAg seroconversion 4) loss of	GlaxoWellcome China

	-allocation concealment; unclear		women of childbearing potential not using effective contraceptive measure. Baseline characteristics Lamivudine (n=322) / Placebo (n=107) Age (mean(SD)) in years: 32.2 (10.3) / 30.8 (9.1) Sex (% men): 239/322 (74%) / 74/107 (69%) Serum HBV DNA (mean (SD)), pg/ml: 96.9 (109.5) / 91.9 (116.5) Serum ALT (mean (SD)), x ULN: 1.7 (2) / 1.5 (1.3)	reasons; none due to adverse events)	reasons; none due to adverse events)		HBeAg 5) Adverse events	

Effect size

Post-treatment (end of 12 weeks)	Lamivudine (100mg/day) (n=293)	Placebo (n=99)	p value
% with undetectable HBV DNA	270/293 (92.2%)	14/99 (14.1%)	P<0.001
Incidence of resistance	Not reported	Not reported	
% with ALT normalisation	91/151 (60.3%)	14/51 (27.5%)	p<0.01
HBeAg loss	23/284 (8.1%)	5/94 (5/3%)	NS
% with HBeAg seroconversion	29/284 (10.2%)	6/94 (6.4%)	NS
% with HBsAg seroconversion	15/293 (5.3%)	4/99 (4.3%)	not stated
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	--
% withdrawn due to adverse events	None		

Authors' conclusion: Lamivudine 100mg daily is very effective in the inhibition of HBV replication indicated by the rapid loss of serum HBV DNA and often accompanied by a decrease of serum ALT levels. Lamivudine is well tolerated without severe adverse events during treatment.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lai 1998	RCT-double blinded Randomisation details not reported. Allocation concealment unclear.	N=358	HBeAg (+) Chinese patients with chronic hepatitis B. Inclusion: Males and females 16 to 70 years old, with detectable HBsAg and HBeAg in serum at the time of screening and for at least the previous 6 months, serum HBV DNA levels of at least 5pg per millilitre, and alanine aminotransferase levels that were less than 10 times the upper limit of normal at screening and for at least the previous 3 months. Exclusion: Patients were excluded if they had hepatitis C or D or HIV infection; decompensated liver disease; or evidence of autoimmune hepatitis (defined as an anti-nuclear titre higher than 1:160). Patients were also excluded if they had received an investigational drug within 30 days before enrolment; any systemic antiviral therapy, immunomodulators, cytotoxic agents, or corticosteroid within 6 months; or lamivudine within 3 months. Baseline characteristics Characteristic / Placebo (n=72) / Lamivudine 25 mg (n=142) / Lamivudine 100 mg (n=143) Age (yr) median / 29 / 33 / 31 Male sex (%) / 72 / 73 / 74 Abnormal / 50 (69) / 98 (69) / 95 (66)	100 mg of lamivudine orally once daily 12 months (n=143) 25 mg of lamivudine orally once daily for 12 months (n=142) – not standard dose No losses to follow up.	Placebo orally once daily for 12 months (n=73) 1 patient wasfound to be ineligible..	52 weeks of treatment	% of patients with undetectable HBV DNA (Abbott solution-hybridization assay; lower limit of detection 1.6pg/mL) HBeAg seroconversion Normalization of ALT levels Resistance (genotypic mutation) YMDD	Supported by Glaxo Wellcome Research and Development

			alanine aminotransferase levels –no (%)							Histologic improvement
			Positive for HBeAg- no (%)	71 (99)	142 (100)	143 (100)				
			Positive for HbsAg-no (%)	72 (100)	142 (100)	143 (100)				
			Positive for HBV DNA- no (%)	70 (97)	135 (95)	140 (98)				
			Serum HBV DNA –pg/ml (mean±SD), log10	1.85±0.63	1.67±0.62 p=0.04 vs. placebo	1.80±0.54				

Effect size

Outcomes (end of 52 week treatment)	Placebo (N=72)	Lamivudine 25 mg (N=142) Not standard dose	Lamivudine 100 mg (N=143) Standard dose	p-value
% of patients with undetectable HBV DNA (<1.6pg/ml) on at least one occasion during treatment	23% (16/70)	73% (98/135)	96% (134/140)	P<0.001 for both comparisons
HBeAg seroconversion and undetectable HBV DNA	3/70 (4)	17/135 (13)	22/140 (16)	P=0.02 for comparison between 100mg and placebo
Normalization of ALT levels – no (%)	12/50 (24%)	64/98 (65%)	68/95 (72%)	P<0.001 for either dose of lamivudine as compared with placebo.
Histologic improvement – no (%)	18/72 (25)	70/142 (49)	80/143 (56)	P≤0.001 for either dose of lamivudine as compared with placebo.
Incidence of genotypic YMDD mutation that confer a reduced sensitivity to lamivudine – no (%)	0 (0)	40 (14)		

Genotypic mutations

Analysis of HBV mutations during lamivudine therapy was undertaken with serum samples obtained from 335 patients at week 52. The incidence of genotypic mutations in the YMDD locus that confer a reduced sensitivity to lamivudine was 14% in both lamivudine groups (mixed wild-type and mutant HBV, 9%; mutant HBV alone, 5%). These mutations were not detected in any patients in the placebo group. In the patients with YMDD mutations, HBV DNA and alanine aminotransferase levels did begin to rise but did not reach baseline levels by week 52. YMDD mutations were not associated with a decreased histologic response.

Notes: Baseline HBV DNA higher in placebo group than lamivudine 25mg group (p=0.04) but inclusion of baseline HBV DNA levels in logistic reression analysis of histologic responses did not affect results.

Authors' conclusion:

In a one-year study, lamivudine was associated with substantial histologic improvement in many patients with chronic hepatitis B. A daily dose of 100 mg was more effective than a daily dose of 25 mg.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Schiff 2003	RCT Multi centre, multinational (62 centres in 11 countries) Computer generated randomisation. Partially blinded (all blinded until	N=238	In adult patients with hepatitis B e antigen (HBeAg) positive chronic hepatitis B who had failed interferon therapy previously Inclusion: Eligible patients ≥16 years, had HBsAg > 6 months, HBeAg, hybridisation-assay detectable HBV DNA, ALT ≥1.3 x the upper limit of normal, histologic chronic hepatitis, and previous treatment with ≥240 million units of IFN; IFN must have been completed ≥ 6 months earlier, and patients must have failed IFN for lack of efficacy, not intolerance. Other inclusion and exclusion criteriawere identical to those in previous western lamivudine trials (referenced to Dienstag 1999 and Schalm 2000)	Lamivudine 100 mg/day orally for 52 weeks (LAM:n=119; 110 completed: withdrawals due to AE: 1, lost to follow up: 2, lack of efficacy: 2, other reasons: 4) Third arm	Placebo orally once daily for 52 weeks (n=56; 46 completed; withdrawals due to AE: 4, lost to follow up: 3, lack of efficacy: 1, other reasons: 2)	Week 52 (end of treatment) plus 16 week post-treatment follow up (those who had HBeAg seroconversion stopped treatment at week 52; those who had not in the LAM group	Primary: histological improvement (≥2 point reduction in HAI) HBV DNA (measured by solution hybridisation assay, Abbott, lower limit of detection 1.6pg/mL in US labs and 3.0pg/mL in	Hepatitis Research Fund of the Massachusetts General Hospital; Clinical Research Centre grant from the National Institutes of Health; Mildred Gabron Research

	week 8; IFN was open label; Lamivudine vs. placebo remained blinded throughout)		Baseline characteristics Characteristic / LAM (n=119) / Placebo (n=56) / Lam + IFN (n=63) Age (median, years) (range): 37 (15-70) / 35 (18-64) / 37 (19-76) Gender (male %): 83 / 88 / 71 Ethnicity (%) White: 78 / 88 / 83 Asian: 9 / 5 / 8 Other: 13 / 7 / 10 Median (range) HBV DNA (pg/ml): 111 (UD*-1668) / 80 (UD-1150) / 92 (UD-711) HBeAg positive n (%): 116 (98) / 54 (96) / 63 (100) HBsAg positive n (%): 119 (100) / 56 (100) / 63 (100) Median (range) ALT/ULN**: 2.8 (0.9-23.4) / 2.2 (0.8-14.4) / 2.3 (1.0-17.3) HAI score***: 10 (1-17) / 10 (3-16) / 10 (2-16) Cirrhosis (%): 19 / 22 / 17	comparing lamivudine 100mg daily for 24 weeks: 1st 8 weeks alone then adding interferon α 2b 10MU subcutaneously three times a week for 16 weeks (n=63; 53 completed; withdrawals due to AE: 1, lost to follow up: 5, lack of efficacy: 0, other reasons: 4)		were re-randomised to continue LAM or switch to placebo; those who had not seroconverted in the placebo group continued placebo) Only data to week 52 usable here	European labs) Improvement in necroinflammatory activity Worsening of fibrosis HBeAg loss HBsAg loss HBeAg seroconversion (defined as loss of HBeAg, loss of detectable HBV DNA, and acquisition of anti-HBe) HBsAg seroconversion ALT responses (normal at 2 visits ≥7 days apart) YMDD variant Safety	Fund; Betty and Newell Hale Research Fund of the Massachusetts General Hospital.

			*Undetectable **Upper limit of normal ***Histologic Activity Index				assessments	

Effect size

Outcomes (week 52)	Lamivudine+IFN (n=63)	Lamivudine (n=119)	Placebo (n=56)	p-value
Histological response (≥2 point reduction in HAI)	20/63 (32%)	62/119 (52%),	14/56 (25%)	p=0.002 LAM vs, placebo p=0.01 LAM + IFN vs. LAM only, NS LAM IFN vs. placebo
Improvement in necroinflammatory activity	21/63 (33%)	63/119 (53%)	16/56 (29%)	P=0.01 for both comparisons
Worsening of fibrosis	8/63 (13%)	4/119 (3%)	3/56 (5%)	P=ns for lamivudine vs. placebo and p=0.017 for lamivudine vs. Lamivudine+IFN
HBeAg seroconversion	7/57 (12%)	19/108 (18%)	7/53 (13%)	NS
HBeAg loss	13/63 (21%)	38/116 (33%)	7/54 (13%)	P=0.01 for lamivudine vs. placeb
HBV response during treatment (undetectable HBV DNA in hybridisation assay at 2 visits ≥7 days apart)	56/57 (98%)	102/110 (93%)	23/54 (43%)	
Sustained HBV DNA responses (as above and maintained subsequently with no two consecutive detectable HBV DNA and undetectable HBV DNA at 52 weeks)	13/57 (23%)	60/110 (55%)	9/54 (17%)	P<0.001 for lamivudine vs. placebo and p=0.002 for lamivudine vs. Lamivudine+IFN
Undetectable HBV DNA by PCR	26/48 (54%) (week 24)	34/99 (34%) at 52 weeks	8/47 (17%) at 52 weeks	Not reported
HBsAg loss	4/63 (6%)	2/119 (2%)	Not reported	not reported
Sustained ALT responses through week 52	11/62 (18%)	51/115 (44%)	8/54 (15%)	P<0.001 for lamivudine vs. placel and p=0.005 for lamivudine vs. Lamivudine+IFN
YMDD variant virus	none (denominator not stated)	27/99 (27%)	none (denominator not stated)	not stated

Adverse events :

The safety profile of lamivudine was similar to that of placebo. The proportion of patients experiencing adverse events was greatest in Lamivudine+IFN, reflecting interferon side effects.

45 serious adverse events were reported in 24 patients; 32/45 (71%) were judged by investigators as unrelated/unlikely to be related to study treatment. Among events considered attributable/possibly attributable to study medication, no difference in pattern occurred between lamivudine and placebo recipients.

Authors' conclusion:

Lamivudine for 52 weeks is as effective in interferon nonresponders as in previously reported treatment naïve patients; however, a combination of lamivudine for 24 weeks and interferon for 16 weeks was not effective in this population.

E.6.1.2 Lamivudine vs placebo (advanced fibrosis or cirrhosis but not decompensation)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Liaw 2004	RCT Randomisation method: unclear Blinding: Partially double blind (see Notes section) Allocation concealment: centrally	N= 651	Largely HBeAg (+) (58%) patients with histologically confirmed cirrhosis or advanced fibrosis (98% Asian) (without evidence of liver decompensation) Inclusion: over 16y with CHB with at least 6 months HBeAg positivity; HBeAg positive or negative with detectable HBV DNA at screening, had had a liver biopsy showing an Ishak fibrosis score of at least 4 at screening or during the previous 2 years. Setting: multicentre international (41 sites) Exclusion: evidence of HCC (suspicious foci on	LAM (100mg/day) (n=436) Median duration of treatment: 32.4 months* *71% patients had received study medication for at least 30	Placebo (n=215) Median duration of treatment: 32.4 months* Did not specify no.	24-30 months post treatment * Study was terminated after a median duration of treatment of 32.4	Time to disease progression (decompensation, hepatocellular carcinoma (HCC), spontaneous bacterial peritonitis, bleeding gastro-oesophageal varices, death related to	GSK (Data were collected by the investigators and analysed by GSK)

	randomised Sample size calculation reported: 240 endpoints required to detect a difference from 20% to 13.3% in the annual rate of disease progression for 90% power with 2:1 assignment and a 25% drop out rate over 5 years giving a sample size of 600 ITT analysis		hepatic ultrasonography at screening or a rising serum level of alpha-fetoprotein), serum ALT >10 x ULN, any evidence of liver decompensation, autoimmune hepatitis, coinfection with HCV or HDV or HIV, other serious concurrent illness, pancreatic amylase or lipase levels >2 x ULN, elevated serum creatinine level, a haemoglobin level of <8g/dL, WBC count <1500 per cubic mm, a platelet count of <50,000 per cubic mm, treatment with immunomodulatory or chronic AV therapy within the 6 months before screening, treatment with any investigational drug within the 30 days before study began, or any previous treatment with LAM; pregnant women. Baseline characteristics LAM (n=436) / Placebo (n=215) Median age, years (range): 43 (17-74) / 44 (22-71) Male, n (%): 370 (85) / 182 (85) Asian, n (%): 426 (98) / 210 (98) Median HBV DNA (mEq/ml) (range): 11.7 (<0.7-109,800) / 21.5 (<0.7-4234) Median ALT (U/L) (range): 70 (14-959) / 68 (7-821) HBeAg positive, n (%): 252 (58) / 124 (58) Child- Pugh score, n (%) 5	months when the study was terminated. Lost to follow up/ reasons: Not stated The evidence for each end point was reviewed and confirmed by a blinded clinical end-points committee composed of 3 internationally recognised hepatologists.	of patients in placebo group received open-label LAM.	months due to a sig. difference between treatment groups in the number of end points reached.	liver disease) Mortality ≥ 2 points increase in Child-Pugh score Incidence of resistance (YMDD mutation)	

6 ≥7	 341 (78) 75(17) 20 (5)	 156 (73) 41 (19) 18 (8)
Ishak fibrosis score, n (%) 4 5 6	 176 (40) 127 (29) 133 (31)	 76 (35) 55 (26) 84 (39)
Median alpha-fetoprotein (μg/l) (range)	8.6 (0.7-600)	9.8 (1.2-298)
ALT >1 x ULN, n (%)	338 (78)	171 (80)

Effect size (ITT analysis)

Outcomes assessed at end of follow up	LAM (n=436)	Placebo (n=215)
Increase in the Child-Pugh score, n (%)	15/436 (3.4)	19/215 (8.8)
Incidence of HCC, n/N (%)	17 (3.9)	16 (7.4)
Mortality (during double blind phase*), n (%)	2	unclear (4 died but unclear when)
Resistance (YMDD mutations), n (%)	209/430 (49)	11/214 (5)

*9 patients died while they were receiving LAM, 7 during open-label treatment with LAM, and 7 died during follow up after treatment.Two patients in LAM died during double blind therapy (1 died from pre-existing lymphoma; 1 died after a MI). 14 deaths were attributed to HCC (8 patients) and an increased Child-Pugh Score (6 patients).

Authors' conclusion:. Continuous treatment with lamivudine delays clinical progression in patients with CHB and advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation and the risk of hepatocellular carcinoma.

Notes: The double-blind phase of the study was terminated at the 2nd interim analysis, because results had crossed the predefined boundary for showing efficacy.

During the double-blind phase, treatment was stopped for patients who reached a clinically confirmed end point (disease progression) or had HBeAg seroconversion. Patients who reached an end point were offered open-label lamivudine for one year and patients who had HBeAg seroconversion were followed up after therapy and had the option to receive LAM as an open-label treatment in the event of serologic relapse. If the trial was terminated according to predeclined criteria, patients were to be offered open-label treatment for one year.

Other outcomes reported: 72 patients reached clinical end points (overall disease progression): 34/436 (7.8%) in LAM group and 38/215 (17.7%) in placebo group (HR=0.45, 95% CI 0.28-0.73) (p=0.001). Kaplan-Meier curves of the % patients with disease progression during double-blind treatment and follow up at 3 years after treatment (shown in graphs only).

Incidence of clinical end points according to YMDD mutation status (not extracted).

Entecavir vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yao, 2007	RCT Double blinded placebo-controlled Lamivudine - refractory patients (HBeAg positive or negative) Sample size calculation	145	Inclusion: men and women at least 16y, HBsAg +ve for at least 6 months, HBV DNA ≥10^5 copies/ml by PCR, ALT in the range of normal to ≤10 x ULN, history of prior lamivudine therapy, evidence of lamivudine refractory status (persistent HBV DNA ≥7MEq/mL by branched chain DNA assay or 105 copies/mL by PCR assay after at least 36 weeks of lamivudine or breakthrough viraemia after achieving undetectable HBV DNA following at least 24 weeks of lamivudine or recurrence of viraemia after discontinuing lamivudine after achieving undetectable HBV DNA and HBeAg negative after at least 36 weeks of lamivuidine or YMDD mutation and HBV viraemia); patients must have discontinued lamivudine at least 12	Entecavir (ETV) 1mg daily for 12 weeks N=116 Followed by 36 weeks of open label ETV treatment (ratio: 4:1)	Placebo for 12 weeks N=29 Followed by 36 weeks of open-label ETV treatment	Outcomes at week 12 (end of randomised treatment perio	Mean log reduction of HBV DNA from baseline by PCR assay (limit of detection 300 copies/mL) % with undetectable	Bristol-Myers Squibb Company

	reported No details of randomisation method or allocation concealment		weeks prior to enrolment, required to have compensated liver function, with prothrombin international normalized ratio ≤1.5, serum albumin ≥3.5g/dl, total serum bilirubin ≤2.5 mg/dl; HBeAg +ve or –ve, or had HBeAb (+) disease were eligible. Setting: 5 centres, China Exclusion: coinfection with HIV, hepatitis C or D virus; other forms of liver disease; 12 or more weeks of therapy with a nucleos(t)ide analogue other than lamivudine; therapy with an immunomodulator or nucleos(t)ide analogue (other than lamivudine) with activity against HBV within 24 weeks of randomisation. Baseline characteristics ETV (n=116) / Placebo (n=29) Mean age (range): 34 (16-66) / 38 (19-57) HBeAg (+) (%): 106 (91) / 25 (86) Sex (% men): 87 (75) / 22 (79) Mean serum HBV DNA (SD), log_{10} copies/ml: 8.84 (0.88) / 8.60 (0.8) Range HBV DNA log_{10} copies/ml: 4.89-10.78 / 6.39-9.79 Mean ALT (SD), U/L: 85.04 (96.6) / 104.24 (91.5) Range ALT U/L: 10-760 / 15-350 >1 x ULN (%): 59 (51) / 16 (55) Documented lamivudine resistance mutations (%): 48 (41) / 13 (45) HBV genotype (%)	Total treatment duration = 48 weeks		d); result at week 48 also presented. No follow up	HBV % (<300 copies/ml by Roche PCR assay) % with serum ALT normalisation (≤1 x ULN) % HBeAg seroconversion Incidence of resistance (among those with viral breakthrough) Adverse events *outcomes measured at week12 (ETV vs. placebo), and week 48 (open-label)	

B C D Indeterminate	37 (32) 78 (67) 1(<1) 0	6 (21) 22 (76) 0 1 (3)
Prior IFN-alfa treatment (%)	17 (15)	6 (21)

Effect size

Post-treatment (at week 12)	Entecavir (n=116)	Placebo (n=29)	p value
Mean reduction of HBV DNA from baseline (SE) (log_{10} copies/mL)	4.3 (0.11)	0.15 (0.20)	<0.0001
% with undetectable HBV DNA (<300 copies/ml)	9/116 (8%)	0/29 (0%)	NS
% with ALT normalisation	40/59 (68)	1/16 (6)	<0.0001
No. withdrawn from trial due to adverse events, n (%)	0 (0)	1 (3.4)	not stated
Resistance – genotypic mutation	0	0	

Notes: also reported results at 48 weeks (open label study – both groups received ETV).

Resistance

Thirteen patients demonstrated virologic breakthrough during 48 weeks of ETV treatment and no genotypic mutation (substitution) was found, suggesting that the observed virologic breakthroughs were not due to the emergence of genotypic resistance to ETV.

Authors' conclusion: Lamivudine-refractory CHB patients treated with entecavir demonstrated marked HBV DNA reduction and normalisation of ALT in most cases. Entecavir treatment for 48 weeks was well tolerated.

Interferon α vs. no treatment

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Mazella 1999 Long term follow up of Saracco 1989	RCT	N=64	HBeAg positive chronic hepatitis B Inclusion: HBeAg positive, HBsAg positive, HBV DNA positive; ALT raised and histological evidence of chronic active or persistent hepatitis by live biopsy; HBcAg (core) in heptaocytes at biopsy Exclusion: Patients younger than 18 years or older than 65 years, pregnant women, histologically proven liver cirrhosis, HDV or HIV antibodies, history of drug abuse Baseline characteristics:	Interferon α (5MU/m^2 intramuscularly three times weekly for 6 months, n=33)	No treatment (n=31)	Treatment 6 months; follow up mean 86.4 (6.96) months (treated group) and 79.7 (6.8) months control group (NS)	Complete response: clearance of HBV DNA (PCR assay, lower limit of detection 100 copies/mL, clearance of HBeAg, seroconversion to anti-HBs, normalisation of ALT	Drug supplied by Glaxo-Wellcome Verona, Italy; no other funding stated

	Interferon α (n=33)	No treatment (n=31)
Gender m/f	25/8	25/6
Median (range) age (years)	36.3 (18-64)	40.6 (18=65)
Median ALT (U/L	106 (51)	144 (90), p=0.02

Effect size

At end of follow up mean 86.4 (6.96) months (treated group) and 79.7 (6.8) months control group unless stated otherwise	Interferon α (n=33)	No treatment (n=31)	p value
Undetectable HBV DNA	26/33 (78.8%)	18/31 (58.1%)	p=0.106

HBeAg loss	30/33 (90.1%)	19/31 (61.3%)	p=0.007
HBeAg seroconversion (developed anti-HBeAg)	20/33 (60.6%)	18/31 (58.1%)	NS
HBsAg loss and seroconversion (developed anti-HBsAg)	12/33 (36.4%)	3/31 (9.7%)	p=0.017
ALT normalisation	22/33 (67%)	11/31 (35.5%)	p=0.025
Cirrhosis-free after 18 months of follow up	29/33 (87.9%)	29/31 (87.1%)	

Notes:

Authors' conclusion: Chronic HBV patients responding to interferon had a faster, more complete and sustained clearance of viral markers than controls.

Entecavir vs entecavir + tenofovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lok 2012	RCT Open label Multicentre Central randomisation centre with interactive voice response system; stratified by site and	379	Nucleos(t)ide naive patients with hepatitis B (e antigen positive or negative) 69 centres from 13 countries Inclusion: male or female, aged 16 years or older, HBeAG + or – CHB (HBsAg at screening and for ≥24 weeks before, or HBsAg <24 weeks plus negative immunoglobulin M core antibody), compensated liver function (INR ≤1.5, albumin ≥3g/dL, bilirubin ≤2.5mg/dL, HBV DNA >172,000 IU/mL (around 10^6 copies/mL) if HBeAg + or >17,200 (around 10^5 copies/mL) if HBeAg -, ALT ≥1.3 x ULN and ≤10 x ULN at screening and at least once ≥12 weeks before. No further exclusion criteria stated.	Entecavir 0.5mg plus tenofovir 300mg daily for 100 weeks (n=198 randomised, 197 treated) 23 (11.6%) discontinued before week 96 (including 6 lost to	Entecavir 0.5mg daily for 100 weeks (n=186 randomised; 182 treated) 12 (6.5%) discontinued before week 96, NS vs. ETV + TDF	100 weeks treatment, then 24 weeks follow up with treatment at discretion of investigator	Primary: HBV DNA <50IU/mL (around 300 copies/mL) at week 96 (measured by Roche Cobas TaqMan HPS assay – lower limit of detection 10IU/mL [around 58 copies/mL])	

	HBeAg status		Baseline characteristics: <table><tr><th></th><th>ETV + TDF (n=197)</th><th>ETV (n=182)</th></tr><tr><td>Mean (SE) age (yr)</td><td>39 (1.0)</td><td>40 (1.1)</td></tr><tr><td>Male n (%)</td><td>146 (74.1)</td><td>116 (63.7)</td></tr><tr><td>Asian White Black Native Hawaiian/Pacific Islander Other</td><td>102 (51.8) 87 (44.2) 4 (2.0) 1 (0.5) 3 (1.5)</td><td>84 (46.2) 83 (45.6) 10 (5.5) 1 (0.5) 4 (2.2)</td></tr><tr><td>HBeAg + HBeAg -</td><td>138 (70.1) 59 (29.9)</td><td>126 (69.2) 56 (30.8)</td></tr><tr><td>Mean log 10 IU/mL HBV DNA</td><td>7.5 (0.10)</td><td>7.5 (0.11)</td></tr><tr><td>Genotype: A B C D Other Missing</td><td> 36 (18.3) 35 (17.8) 53 (26.9) 57 (28.9) 16 (8.1) 0</td><td> 38 (20.9) 38 (20.9) 35 (19.2) 55 (30.2) 12 (6.6) 4 (3.2)</td></tr><tr><td>Mean (SE) ALT (U/L)</td><td>158 (13.1)</td><td>127 (7.3)</td></tr></table>		follow up; 5 AE)	group (including 7 lost to follow up; 2 AE)		Secondary: HBV DNA <50IU/mL at week 48 and <50IU/mL at week 48 and 96 by HBeAg status, ALT normalisation (≤1 x ULN). HBeAg loss, HBeAg seroconversion, HBsAg loss, virological breakthrough, drug resistance, adverse events	
Effect size								

	ETV + TDF (n=197)		ETV (n=182)	
	Week 48	Week 96	Week 48	Week 96
HBV DNA <50IU/mL	158/197 (80.2%)	164/197 (83.2%)	128/182 (70.3%) p=0.026	139/182 (76.4%) p=0.088
Mean (SE) HBV DNA mean change from baseline $\log_{10}$ IU/mL	-5.99 (0.10)	-5.96 (0.12)	-5.57 (0.10)	-5.77 (0.11) p=0.25
ALT normalisation	143/197 (72.6%)	136/197 (69.0%)	151/182 (83.0%)	149/182 (81.9%) p=0.004
HBeAg loss (among those HBeAg + at baseline)	27/138 (19.6%)	41/138 (29.7%)	32/126 (25.4%)	49/126 (38.9%)
HBeAG seroconversion (among those HBeAg + at baseline)	25/138 (18.1%)	30/138 (21.7%)	28/126 (22.2%)	41/126 (32.5%)
HBsAg loss	2/197 (1.0%)	7/197 (3.6%)	4/182 (2.2%)	5/182 (2.7%)
HBsAg seroconversion	1/197 (0.5%)	4/197 (2.0%)	1/182 (0.5%)	2/182 (1.1%)
Virological breakthrough		7 (3.6%)		2 (1%)
Resistance mutations		0		0
Discontinued due to adverse events		5		2

Notes: samples size of 384 estimated to provide >80% power to show superiority of ETV + TDF over ETV alone assuming a response rate (noncompleters considered failures) of 85% for combination therapy and 70% for monotherapy among HBeAg + patients and 95% for combination and 90% for monotherapy among HBeAg – paitents (70% of patients HBeAg+ and 30% HBeAg-)

Authors' conclusion: The antiviral efficacy of ETV monotherapy is comparable to that of ETV plus TDF in a mixed population of nucleos(t)ide naive patients with chronic hepatitis B (70% HBeAg positive). The combination therapy could provide an incremental benefit to HBeAg-positive patients with baseline levels of HBV DNA $\geq 10^8$ IU/mL.

Lamivudine vs peg IFN; peg IFN + placebo vs peg IFN + lamivudine; peg IFN + lamivudine vs lamivudine

Reference	Study type	Number of patien	Patient characteristics	Intervention	Comparison	Length of follow-	Outcome measures	Source of funding

		ts				**up**		
Lau 2005	RCT - Partially double blind (blinded in the lamivudine versus placebo part in the two peginterferon arms) Randomisation was centralised and stratified according to geographic region and alanine aminotransferase level. Allocation concealment not reported.	n=814	Patients with HBeAg-positive chronic hepatitis B. Inclusion: Adults were eligible if they had been positive for hepatitis B surface antigen (HBsAg) for at least 6 months, were negative for antibodies to HBsAg and positive for HBeAg, had an HBV DNA level of more than 500,000 copies per millilitre, had a serum alanine aminotransferase level that was greater than 1 but less than or equal to 10 times the upper limit of the normal range, and had had findings on a liver biopsy within the previous 12 months that were consistent with the presence of chronic hepatitis B. Setting: Multi centre (67 sites in 16 countries in Asia, Australia, Europe, and North and South America) Exclusion criteria: decompensated liver disease, a co-existing serious medical or psychiatrist illness, a neutrophil count of less than 1500 per cubic millilitre, a platelet count of less than 90,000 per cubic millilitre, a serum creatinine level that was more than 1.5 times the upper limit of the normal range, a history of alcohol or drug abuse within one year before entry, and co-infection with hepatitis C or D virus or HIV virus. Previous treatment for chronic hepatitis B was permitted, but not within the 6 months before the study. Baseline characteristics Characteristic: Lamivudine (n=272); Peginterferon alfa-2a + placebo (n=271); Peginterferon alfa-2a + lamivudine (n=271) Male sex- no (%): 215 (79); 214 (79); 208 (77) Age (yr) mean±SD: 31.6±9.7; 32.5±9.6; 31.7±10.3	100 mg lamivudine once daily for 48 weeks. (n=271) 42 lost to follow up. n=230 in lamivudine completed treatment	180 µg of peginterferon alfa-2a once weekly+ oral placebo once daily for 48 weeks (n=272) 28 lost to follow up. n=243 peginterferon alfa-2a completed treatment Third arm: 180 µg of peginterferon alfa-2a once weekly+ oral lamivudine (n=271); 25 dropped out; 246 completed	Week 48 (end of treatment) and week 72 (end of 24 weeks follow-up)	Primary: HBeAg seroconversion ; % of patients with HBV DNA (<100,000 copies per millilitre) Secondary: combined response (HBeAg seroconversion, normalisation of ALT, HBV DNA < 100,000 copies/mL) HBeAg loss HBV DNA reduction % of patients with HBV DNA (<400 copies per millilitre)	Roche, Basel, Switzerland.

			White Asian Black Other	32 (12) 232 (85) 3 (1) 5 (2)	24 (9) 237 (87) 4 (1) 6 (2)	23 (8) 236 (87) 4 (1) 8 (3)				HBsAg seroconversion % of patients with ALT normalization Histologic improvement Resistance (YMDD genotypic mutation) Adverse events	
			Alanine aminotransferase-IU/litre mean±SD	102.3±78.4	114.6±114.3	114.9±94.1					
			HBV DNA-log copies/ml mean±SD	10.1±2.0	9.9±2.1	10.1±1.9					
			Bridging fibrosis or cirrhosis- no (%)	47 (17)	49 (18)	40 (15)					
			Previous use of conventional interferon alfa- no (%)	32 (12)	30 (11)	32 (12)					
			Previous use of lamivudine- no (%)	42 (15)	31 (11)	24 (9)					
			Genotype A B C D E, F or H Mixed	 15 (6) 73 (27) 162 (60) 17 (6) 4 (1) 1 (<1)	 23 (8) 76 (28) 162 (60) 9 (3) 0 1 (<1)	 18 (7) 82 (30) 156 (58) 11 (4) 3 (1) 1 (<1)					

Effect size

Outcomes- end of treatment (week	peginterferon alfa-2a	peginterferon alfa-2a +	Lamivudine (n=272)	Diffference between groups

48)	+ placebo (n=271)	lamivudine (n=271)		
HBeAg seroconversion no (%)	72/243	64/246	55/230	p=0.003 for the overall test of treatment effect, and p=0.23 for the comparison between peginterferon alfa-2a plus placebo and peginterferon alfa-2a plus lamivudine
HBeAg loss – no (%)	81/243	73/246	59/230	not stated
No (%) of patients with HBV DNA <100,000 copies/ml)	142/243	233/246	169/230	p=0.007 for the overall test of treatment effect, and p=0.65 for the comparison between peginterferon alfa-2a plus placebo and peginterferon alfa-2a plus lamivudine
Patients – no (%) HBV DNA< 400 copies/ml (assumed lower limit of detection but not stated)	68/243	186/246	108/230	not stated
Mean change in HBV DNA log copies/ml	-4.5 (-4.1 to -4.9) n=248	-7.2 (-6.9 to -7.5) n=249	-5.8 (-5.4 to -6.1) n=249	
Patients – no (%) Normalisation of ALT	105/243	126/246	168/230	not stated
Resistance – YMDD mutation (%)	not tested	69/254 (27)	9/256 (4)	p<0.001
Discontinuation for safety reasons –no (%)	8/243	12/246	2 /230	p=0.03 for the overall test of treatment effect. P=0.06 for the comparison between peginterferon alfa-2a plus placebo and lamivudine alone, and p=0.01 for the comparison between peginterferon alfa-2a plus lamivudine and lamivudine alone
Outcomes- end of follow-up (week				

72)				
Patients – no (%) HBeAg seroconversion	87/243	74/246	52/230	p<0.001 peginterferon alfa-2a + placebo vs. lamivudine; p=0.02 peginterferon alfa-2a + lamivudine vs. lamivudine
Patients – no (%) HBeAg loss	91 /243	77/246	57/230	p<0.001 peginterferon alfa-2a + placebo vs. lamivudine; p=0.04 peginterferon alfa-2a + lamivudine vs. lamivudine
Patients – no (%) with HBV DNA (<100,000 copies/ml)	86/243	91/246	60/230	p=0.01 peginterferon alfa-2a + placebo vs. lamivudine; p=0.003 peginterferon alfa-2a + lamivudine vs. lamivudine
Patients – no (%) HBV DNA < 400 copies/ml	39/243	37/246	14/230	p<0.001 peginterferon alfa-2a + placebo vs. lamivudine; p<0.001 peginterferon alfa-2a + lamivudine vs. lamivudine
Mean change in HBV DNA log copies/ml	-2.4 (-2.0 to -2.8) n=248	-2.7 (-2.2 to -3.1) n=254	-1.9 (-1.5 to -2.3) n=241	
Patients – no (%) Normalisation of ALT	111/243	106/246	76/230	p=0.002 peginterferon alfa-2a + placebo vs. lamivudine; p=0.006 peginterferon alfa-2a + lamivudine vs. lamivudine
Histologic improvement (among those with paired biopsy samples)	102/207	112/215	93/184	not stated

Notes life threatening hepatic encephalopathy developed in one patient who died, which was considered by the investigator to be related to discontinuation of lamivudine treatment.

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Sample size of 231 patients per treatment arm provided at least 80% power at 0.0125 level with a two-sided test to detect a difference in HBeAg seroconversion rates of 20% vs. 34% or HBV DNA suppression <100,000 copies/mL of 30% vs. 45%; the sample size was increased to 250 to allow for withdrawals. Patients with missing values at week 72 were classified as having missing values.

Authors' conclusion:

In patients with HBeAg-positive chronic hepatitis B, peginterferon alfa-2a offers superior efficacy over lamivudine, on the basis of HBeAg seroconversion, HBV DNA suppression, and HBsAg seroconversion.

Telbivudine vs adefovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chan HLY, Heathcote EJ, Marcellin P et al. 2007	RCT Centralised computer generated process. Allocation concealment implicit in the process. "Brittle nature of the adefovir tablets precluded treatment blinding by routine overencapsulation". Investigators blinded to HBV serologic data from baseline to	N= 136	HBeAg positive patients Inclusion: HBeAg/ HBsAg +ve; CHB; 18-70 yrs; no Hx or signs of hepatic decompensation; ALT between 1.0 and 1.3 and 10 times ULN; serum HBV DNA > 6 $\log_{10}$ copies/mL. Setting: 16 outpatient clinics in Hong Kong, Australia, Canada, France, Korea, Singapore, Taiwan, Thailand and US. Predominantly Asian ethnicity. Exclusion: Pregnant; breastfeeding; co-infection with Hep C/D or HIV; other causes of liver disease; Hx or signs of pancreatitis or liver carcinoma; potentially confounding medical conditions; previous treatment with nucleoside or nucleoside analogues, or had received interferon or other immunomodulatory agents within 12months of screening; alcohol/illicit drug use within past 2 yrs; elevated serum creatinine levels; Hb<110 g/L (men) or <100 g/L (women); absolute neutrophil count of <2x10^9 cells/L, platelets < 1 x 10^{11}, alpha fetoprotein levels > 50 microg/L; serum amylase or lipase >1.5 x ULN; prothrombin time prolonged by > 3 secs above ULN; albumin <34g/L; bilirubin 2 x ULN. Baseline characteristics: Reported to be well matched.	Telbivudine 600mg/day (Group A: n=45) Total duration of treatment: 52 weeks Loss to follow up/reasons: ALL received Rx, but 2 discontinued at >24 weeks (pregnancy and investigator request). 45 analysedweek 24 and 43	Adefovir 10 mg/day (Group B: n=45) Total duration of treatment: 52 weeks Loss to follow up/reasons: 44/45 received Rx (1 withdrew consent), and 2 discontinued (1 at <24 and 1 at >24 weeks, both due to non adherence). 43	At week 24: primary treatment comparison was telbivudine (group A) versus pooled adefovir (groups B and C). Also group A vs. Group B vs. Group C at 52 weeks. No	Log reduction of HBV DNA % with undetectable HBV DNA (<300 copies/mL) measured by PCR assay Incidence of resistance (genotypic mutation and viral breakthrough) % with ALT normalisation % with HBeAg loss and/or seroconversion	Idenix pharmaceuticals and Novartis Pharmaceuticals

	week 52. Staff from 3rd party agency collected and analysed data, but not stated if they were blinded to group status of samples. Target sample size 120 provided 98% power to detect a difference of 1.5 log_{10} copies/mL in HBV DNA reduction at week 24		<table><tr><th></th><th>TEL n=45</th><th>ADE n=44</th><th>Adefovir then telbivudine n=46</th></tr><tr><td>Mean age (range)</td><td>34 (18-60)</td><td>30 (19-47)</td><td>33 (18-53)</td></tr><tr><td>Mean weight (se), kg</td><td>68 (2)</td><td>69 (1.8)</td><td>63 (1.7)</td></tr><tr><td>Sex (n % men)</td><td>35 (78%)</td><td>40 (91%)</td><td>27 (59)</td></tr><tr><td>Mean serum HBV DNA (se), log_{10} copies/ml</td><td>9.57 (0.26)</td><td>9.98 (0.23)</td><td>9.47 (0.29)</td></tr><tr><td>Median serum ALT (range), U/L</td><td>133 (47-750)</td><td>144 (43-854)</td><td>110 (50-455)</td></tr><tr><td>Asian White Other</td><td>42 (93) 3 (7) 0</td><td>39 (89) 1 (2) 4 (9)</td><td>43 (94) 1 (2) 2 (4)</td></tr></table>					

Effect size

Post treatment (52 weeks)	TEL (600 mg/day) (n=43)	ADE (10 mg/day) (n= 42)	Adefovir followed by telbivudine n=46	p value telbivudine versus adefovir
Log reduction of HBV DNA	6.56	5.99	6.44	p=0.012
% with undetectable HBV DNA	60% (26/43)	40% (17/42)	54% (25/46)	1.89 (0.72, 4.94) NS
Viral breakthrough (>1 log_{10} above the nadir value), n	3	4	0	
Incidence of resistance (telbivudine	3/43	0/42	Not reported	Not reported

genotypic mutation)				
Incidence of resistance (codon A181V/T or N236T signature resistance mutations in ADV recipients) with viral breakthrough	0	0	Not reported	
% with ALT normalisation	79% (34/43)	85% (36/42)	85% (39/46)	NS
% with HBeAg loss	30% (13/43)	21% (9/42)	26% (12/46)	NS
% with HBeAg seroconversion	28% (12/43)	19% (8/42)	24% (11/46)	NS
% with HBsAg loss and/or seroconversion	none	none	none	
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported	
% withdrawn due to adverse events	0	0	0	

Authors' conclusion:Telbivudine demonstrated greater and more consistent HBV DNA suppression than adefovir after 24 weeks of treatment. After 52 weeks, HBV DNA suppression was greater in patients who had received continuous telbivudine or were switched to telbivudine after 24 weeks than those who received continuous adefovir.

Notes: Used a difference of 1.5$\log_{10}$ copies/mL in HBV DNA reduction at week 24 for sample size calculation. These are based on previous study results, not MIDS, however. Switching from adefovir to telbivudine was also reported in the paper, not covered in this review.

Entecavir vs lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chang 2006	RCT Treatment assignments allocated centrally on	N=715	Patients with HBe antigen (HBeAg) positive chronic hepatitis B. Setting: Multicentre (137 centres worldwide including 41 centres in Europe, 40 in N. America, 26 in Asia, 12 in Australia and 18 South America).	Entecavir 0.5 mg once daily for a minimum of 52 weeks (n=357)	Lamivudine 100 mg once daily for a minimum of 52 weeks. (n=358)	At week 48 of treatment	Primary: Histologic improvement (at least 2 point improvement in Knodell necroinflamm	Bristol-Myers Squibb

	the basis of permuted block sizes of four that were assigned within each centre. Double blind.		Inclusion: Patients were 16 years of age or older and had HBeAg-positive chronic hepatitis B and compensated liver function (a total serum bilirubin level of 2.5 mg per decilitre [42.8 µmol per litre] or less; a prothrombin time not more than 3 seconds longer than normal or an international normalised ratio not greater than 1.5; a serum albumin level of at least 3g per decilitre; and no history of variceal bleeding or hepatic encephalopathy). Eligible patients also had detectable hepatitis B surface antigen (HBsAg) for at least 24 weeks before screening, evidence of chronic hepatitis on a baseline liver biopsy specimen obtained within 52 weeks before randomisation, evidence of HBV DNA by any commercial assay at least 4 weeks before screening, an HBV DNA level of at least 3 MEq per millilitre by the branched chain DNA assay at screening and a serum alanine aminotransferase level 1.3 to 10 times the upper limit of normal at screening. Exclusion: Co-infection with hepatitis C, hepatitis D, or HIV; the presence of other forms of liver disease; use of interferon alfa, thymosin alpha or antiviral agents with activity against hepatitis B within 24 weeks before randomisation; prior lamivudine therapy lasting more than 12 weeks; an alpha fetoprotein level greater than 100 ng per millilitre; a history of ascites requiring diuretics or paracentesis; and previous treatment with entecavir. Baseline characteristics	354 received treatment 340 patients assigned to the entecavir group (95%) completed 52 weeks of treatment. 1 discontinued due to adverse events; 3 lost to follow up	355 received treatment 321 patients assigned to the lamivudine group (90%) completed 52 weeks of treatment. 9 discontinued due to adverse events; 8 lost to follow up		atory score with no worsening in fibrosis score) at week 48 Secondary: Log reduction in HBV DNA level % patients with undetectable HBV DNA (<300copies/ml; lower limit of detection), as measured by the Roche COBAS Amplicor PCR assay % HBeAg loss % HBeAg seroconversion % HBsAg loss Normalisation of alanine	

			Characteristic	Entecavir (n=354)	Lamivudine (n=355)				aminotransferase level. Resistance (viral breakthrough) Resistance (YMDD genotypic mutation) Adverse events	
			Age (yr)	35±13	35±13					
			Male sex-no (%)	274 (77)	261 (74)					
			Knodell necroinflammatory score	7.8±2.98	7.7±2.99					
			Ishak fibrosis score	2.3±1.27	2.3±1.29					
			Mean HBV DNA level By branched chain DNA assay-MEq/ml By PCR assay-log copies/ml	2.56±1.05 9.62±2.01	2.61±1.03 9.69±1.99					
			HBeAg positive- no (%)	348 (98)	351 (99)					
			HBeAg antibody-negative- no (%)	342 (97)	346 (97)					
			Alanine aminotransferase-IU/litre	140.5±114.3	146.3±132.3					
			Asian White Black Other	204 (58) 140 (40) 8 (2) 2 (<1)	202 (57) 141 (40) 8 (2) 4 (1)					
			Genotype:							

			A B C D F Other	94 (27) 68 (19) 111 (31) 37 (10) 20 (6) 24 (7)	100 (28) 77 (22) 90 (25) 49 (14) 12 (3) 27 (8)				
			Prior interferon n (%)	46 (13)	46 (13)				
			Prior lamivudine n (%)	10 (3)	10 (3)				

Effect size (available case analysis)

Outcomes – at week 48	Entecavir (n=340)#	Lamivudine (n=321)#	Difference estimate (95% CI)	p-value
HBV DNA <300 copies/ml by PCR assay- no (%)	236/340	129/321		p<0.001
HBV DNA <0.7 MEq/ml by branched chain DNA assay- no (%)	322/340	232/321		p<0.001
Mean change in HBV DNA from baseline by PCR assay- log copies/ml	-6.9±2.0	-5.4±2.6	-1.52 (-1.78 to -1.27)	<0.001
Histologic improvement – no*	226/292	195/269	9.9 (2.6 to 17.2)	0.009
Mean Knodell necroinflammatory score**	4.4	4.6	Not reported	Not reported
Improved Ishak fibrosis score -%	39%	35%	Not reported	0.41
ALT normalisation (≤1 x ULN)- no. (%)	242/340	213/321	8.4 (1.3 to 15.4)	0.02
Loss of HBeAg- no. (%)	78 (22)	70 (20)	2.3 (-3.7 to 8.3)	0.45
HBeAg seroconversion- no. (%)	74 (21)	64 (18)	2.9 (-2.9 to 8.7)	0.33
HBsAg loss –no. (%)	6 (2)	4 (1)	0.6 (-1.2 to 2.3)	0.52
Viral breakthrough – no (%)	6 (2)	63 (18)		

Resistance (YMDD mutation) in patients with viral breakthrough – no (%)	0/6	45/63 (71)		
Discontinuation due to adverse event ALT >2 x baseline and >10x ULN ALT >2 x baseline and >5 x ULN	1 (<1) 12 (3) 37 (10)	9 (3) 23 (6) 59 (17)	Not reported	0.02 0.08 0.02

#There were 340 patients in ETV group and 324 patients in the LAM group with paired baseline and week 48 HBV DNA measurements

Authors' conclusion: Among patients with HBeAg-positive chronic hepatitis B, the rates of histologic, virologic and biochemical improvement are significantly higher with entecavir than lamivudine.

Follow up studies (of the included RCTs)

Reference	Study type	No. patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chang TT, 2009	RCT. 2 year follow up to Chang 2006 No mention of randomisation method or allocation concealment (although this may be described in Chang 2006). 52 week blinded RX phase, followed by an extended	709 patients randomised to entecavir (n=354) or lamivudine (n=355). Those eligible to continue to the second phase (post 52 weeks) were the virological responders from each group only	Inclusion and Exclusion: Described in Chang 2006 Baseline characteristics. Not given. Likely to be in Chang 2006.	Entecavir (ETV) 0.5 mg/day. For 52 weeks, then an additional 44 for virological responders Loss of 14 from ETV by week 52 (reasons not given). A further loss of	Lamivudine (LMV) 100mg/day.. For 52 weeks, then an additional 44 for virological responders Loss of 29 from LMV at week 52 (reasons not given). A	2 years	Serum HBV-DNA HBeAg status Serum ALT. Histologic improvement after 48	not stated

	blinded treatment phase for up to 44 additional weeks (96 in total). Only those deemed to have a "virological response" [partial response to treatment] continued to this phase. These patients had an HBV-DNA of <0.7 MEq/mL but without loss of HBeAg. In contrast complete responders (Those with HBV-DNA of <0.7 MEq/mL AND loss of HBeAg) were withdrawn from treatment and monitored for 24 weeks. Non-responders (a HBV-DNA of >0.7 MEq/) were also withdrawn and given alternative treatment.	(ETV n=247, LMV n=165).		4 from the ETV group occurred during the second phase. An ITT approach used, with missing data imputed as a failure.	further loss of 1 from the LMV group occurred during the second phase.		weeks of treatment, defined as a >2 point improvement in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score.	

Results: ALL ITT, with no data classed as treatment failures.

Outcome	ETV	LMV	p
FIRST PHASE (YR 1 RESULTS) – ALL SUBJECTS			
Reduction in HBV-DNA (log10 copies/mL) week 48	-6.9 (no variance given but can estimate sds based on p value of 0.0001)	-5.4 (no variance given but can estimate sds based on p value of 0.0001)	<0.0001
HBV-DNA <300 copies/mL week 48	67% (237/354)	36% (128 /355)	<0.0001
Serum ALT level < 1 x ULN week 48	68%(241/354)	60%(213 /355)	0.02
Histologic improvement - defined as a >2 point improvement in the Knodell necroinflammatory score with no worsening in the Knodell fibrosis score. Week 48	72% (/354)	62% (/355)	0.0085
HBeAg loss week 48	22%(78/354)	20%(71/355)	0.45

HBeAg seroconversion week 48	21%(74 /354)	18%(64 /355)	0.33
HBsAg loss week 48	2%(7/354)	1%(4 /355)	0.52
SECOND PHASE (YR 2 RESULTS)- VIROLOGIC RESPONDERS ONLY UNLESS STATED			
HBV-DNA <300 copies/mL week 48	64% (156/243)	40% (66/164)	
HBV-DNA <300 copies/mL at end of dosing (EOD)	74% (180/243)	37% (60/164)	
ALT normalisation week 48	66% (161/243)	71% (116/164)	
ALT normalisation at EOD	79% (183/243)	68% (112/164)	
HBe seroconversion at EOD [as pts with HBeAg loss at the end of yr1 discontinued reatment, this variable is incremental to that reported in yr1].	11% (26/243)	12% (20/164)	
Cumulative proportions of ALL patients achieving HBV-DNA <300 copies/mL	80% (283/354)	39%(138/355)	
Cumulative proportions of ALL patients achieving ALT normalisation	87%(308 /354)	79%(280/355)	
Cumulative proportions of ALL patients achieving HBeAg seroconversion	31%(110/354)	25%(89/355)	
Cumulative proportions of ALL patients achieving HBsAg loss	5%(18/354)	3%(11/355)	
Cumulative proportions of ALL patients achieving HBsAg seroconversion	2%(7/354)	2%(7/355)	
Discontinuation due to adverse events	1/354	9/355	

NOTES:

Prev Rx or naive: unclear

Duration: 52 weeks for all, then an additional 44 weeks for virological responders

No co-infections

Setting: Single centre study in Taiwan.

Predominant genotype: not stated

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of

								fundi ng
Shouval D, 2009	RCT. (Follow up to Lai et al. N Eng J Med 2006; 345: 1011-1020). Double blind multicentre trial. No mention of randomisation method or allocation concealment (although this may be described in Lai 2006). 52 week initial RX phase, followed by an extended treatment phase for up to 44 additional weeks (96 in total). Only those deemed to have a "virological response" [partial response to treatment] continued to this phase. These patients had an HBV-DNA of <0.7 MEq/mL but without ALT <1.25 x ULN. In contrast complete responders (Those with HBV-DNA of <0.7 MEq/mL AND ALT <1.25 x ULN) were eligible to be withdrawn from treatment and monitored for 24 weeks. Non-responders (a HBV-DNA of >0.7 MEq/) were also eligible to be withdrawn and given alternative treatment.	N=638 Those eligible to continue to the second phase (post 52 weeks) were the virological responders from each group only (ETV n=26, LMV n=28). A further loss of 8 from the ETV group and 6 from the LMV group occurred prior to beginning the second phase (but after the first phase). In addition, there were reports of further withdrawal from therapy for 2 ETV and 8 LMV patients. Reasons were: loss to FU: ETV 1, LMV 1; lack of efficacy ETV 0 LMV 6; no longer met study criteria: ETV 1 LMV 1. An ITT approach used (though for the specific yr 2 results this does not encompass those lost just before the second phase).	Inclusion and Exclusion: >16 yrs of age; compensated liver function; detectable HBsAg for at least 24 weeks prior to screening; evidence of CHB by liver biopsy at baseline; HBV-DNA > 0.7 MEq/mL and ALT of 1.3-10 x ULN Baseline characteristics. Most provided in Lai 2006. Baseline characteristics of the two Yr 2 virological responders groups: ETV: HBV-DNA (log10 copies/mL) 7.66; ALT (IU/L) 157.1 LMV: HBV-DNA (log10 copies/mL) 7.52; ALT (IU/L) 139.5	Entecavir (ETV) 0.5 mg/day (n=325) For 52 weeks, then an additional 44 for virological responders Loss of 13 from ETV by week 52	Lamivudine (LMV) 100mg/day (n=313) For 52 weeks, then an additional 44 for virological responders Loss of 16 from LMV at week 52 (reasons not given)	52 weeks, up to 96 weeks	Proportion of complete responders by 52 weeks Sustenance of total response Proportion of virological responders achieving <300 copies/mL in the 2nd year Proportion of virological responders achieving ALT normalisation in the 2nd year Resistance	not stated

							analysis	

Results:

Outcome	ETV	LMV	p
Proportion with a full response (HBV-DNA of <0.7 MEq/mL AND ALT <1.25 x ULN) by 48 weeks	275/325	245/313	
Proportion of those with full response who had ALSO got HBV-DNA <300 copies/mL at week 48	257/275	201/245	
Proportion of those with all 3 measures of response (HBV-DNA of <0.7 MEq/mL AND ALT <1.25 x ULN AND HBV-DNA <300 copies/mL) who maintained <300 copies/mL through the 24 weeks of non-Rx monitoring	7/257 (3%)	10/201 (5%)	
Proportion of those with full response who had ALSO got ALT < 1x ULN at week 48	249/275	216/245	
Proportion of those with both measures of response (HBV-DNA of <0.7 MEq/mL AND ALT <1.00 x ULN) who maintained < 1x ULN through the 24 weeks of non-Rx monitoring	121/249 (49%)	84/216 (39%)	
2ND YR RESULTS			
Achievement of HBV-DNA <300 copies/mL by week 48 in virological responders	26/26 (100%)	18/28 (64%)	
Maintenance of <300 copies/mL by EOD	22/26 (85%) [Of the 4 not maintaining <300 copies, 3 had missing data and were therefore imputed failures]	16/28 (57%) [Of the 12 not maintaining <300 copies, 5 had missing data and were therefore imputed failures]	
Proportion of virological responders achieving ALT < 1 x ULN by EOD	7/26 (27%)	6/28 (21%)	
Proportion of virological responders achieving HBsAg loss	0	0	
virological breakthrough and resistance			
emergence of resistance in patients:	1/26 [this patient had resistance to ETV but not explicitly stated (s)he was in the ETV group]	0/28	

Virological breakthrough (> 1 log10 increase in HBV-DNA level above nadir, determined by 2 sequential measurements) occurring throughout the 96 weeks	8/325 [genotype analysis failed to show evidence of ETV resistant substitutions in these patients]	36/313	
Discontinuation due to adverse effects	6/325 (2%)	9/313 (3%)	

NOTES:
Prev Rx or naive: unclear
Duration: 52 weeks for all, then an additional 44 weeks for virological responders
No co-infections
Setting: International multicentre study.
Predominant genotype: not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ren 2007	RCT Details of randomisation, allocation concealment not reported. Blinding	N=42	Hepatitis B e antigen (HBeAg)-positive chronic hepatitis B patients (groups A and B) who had not received a nucleoside analogue (and a third group [C] who had failed in lamivudine therapy). Inclusion: Patients aged between 19 and 68 years and had HBeAg-positive chronic hepatitis B and compensated liver function: a total serum bilirubin level of 2.5 mg decilitre or less; a prothrombin time not more than three seconds longer than normal or a ratio not greater than 1.5; a serum	Entecavir 0.5 mg/day (group B) for 48 weeks. (n=21)	Lamivudine 100mg/d (group A) for 48 weeks. (n=21) 1 withdrew from trial	At week 48.	Log reduction of HBV DNA - analysis measured by PCR analysis % patients with undetectable HBV DNA (by PCR, lower limit of	None reported

	not reported. ITT analysis China		albumin level of at least 3.0 g per decilitre; and no history of variceal bleeding or hepatic encephalopathy. Eligible patients also had detectable hepatitis B surface antigen (HBsAg) for at least 24 weeks before screening, evidence of HBV DNA by any commercial assay at least 4 week before screening, and a serum alanine aminotransferase level 1.3 -10.00 times that of the upper limit of normal at screening. Exclusion: Co-infection with hepatitis C, D, or the HIV virus, the presence of other liver diseases; use of interferon, thymosin, antiviral agents with activity against hepatitis B within 24 week before randomisation; prior lamivudine therapy lasting more than 12 week; an alpha fetoprotein level greater than 100mg/ml; a history of ascites requiring diuretics or paracentesis; and previous treatment with entecavir and adefovir. Baseline characteristics <table><tr><th>Characteristic</th><th>Lamivudine 100 mg/d (group A) (n=21)</th><th>Entecavir 0.5 mg/d (group B) (n=21)</th><th>Entecavir 1 mg/d (group C) (n=19</th></tr><tr><td>Age (yr)</td><td>31±12</td><td>33±10</td><td>31±11</td></tr><tr><td>Sex (M/F)</td><td>11/10</td><td>12/9</td><td>11/8</td></tr><tr><td>HBV DNA (log copies/ ml)</td><td>8.49±1.10</td><td>8.52±1.02</td><td>8.60±0.90</td></tr><tr><td>ALT (IU/L)</td><td>201.6±178.2</td><td>211.2±144.7</td><td>198.9±1695</td></tr></table>		at 32 weeks		detection not stated) Normalisation of ALT % HBeAg loss and seroconversion Adverse events	

Effect size (ITT analysis)

	Entecavir 0.5 mg/d (n=21) (Group B)	Lamivudine 100 mg/d (n=21) (Group A)	p-value
Outcomes – at week 48			
Undetectable HBV DNA levels by PCR, (%)	15/21	8/21	P <0.0001
Mean reduction in the serum HBV DNA levels (log copies/ml)	5.9	4.2	<0.001
Rate of HBeAg seroconversion, %	3 (15)	4 (18)	Not reported
Normalisation of ALT levels %	18 (85.7)	16 (76.2)	Not reported

Authors' conclusion:

Entecavir had a significantly higher response rate than lamivudine in patients with HBeAg positive chronic hepatitis B patients who had not previously received a nucleoside analogue; entecavir can effectively inhibit the replication of HBV DNA and normalise the levels of ALT in refractory chronic hepatitis B patients treated with lamivudine; and entecavir is safe in clinical application.

Note: did not define undetectable HBV DNA and ALT normalisation. Study also included group C – switching from LAM to ETV (non-randomised).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Shindo 2009A	RCT (phase II)	N=137	Hepatitis B e antigen (HBeAg)-positive or negative chronic hepatitis B patients who had not received a nucleoside analogue	Entecavir 0.5 mg/day for 24	Lamivudine 100mg/d for 24	At week 22	Primary: Change from baseline in	None reported

	Details of randomisation not reported (except stratified by HBeAg status); allocation concealment not reported Double Blind ITT analysis Multicentre Japan		Inclusion: Patients aged between 20 and 75 years, men and women, hepatitis B surface antigen (HBsAg) for at least 24 weeks or IgM HBcAb-negative with biopsy-confirmed CHB; Hepatitis B e antigen (HBeAg)-positive or negative for 12 weeks or more; HBV DNA ≥40MEq/mL measured 2 weeks or more before screening and at screening; serum ALT 1.25-10 times ULN; well-compensated liver disease: a prothrombin time not more than three seconds longer than normal or a ratio not greater than 1.5; a serum albumin level of at least 3.0 g per decilitre; a total serum bilirubin level of 2.5 mg decilitre or less Exclusion: Pregnant women; latients with liver cirrhosis; history or evidence of variceal bleeding, hepatic encephalopathy or ascites requiring diuretics, or paracentesis, other liver diseases; serum creatinine >1.5 x ULN, Hb <10g/dL, platelet count <70,000/mm^3, granulocyte count <1,500/mm^3 or plasma alpha fetoprotein level greater than 100mg/ml; allergy induced by nucleoside analog, recent (within 24 weeks) history of immunosuppressives or interferon-α/β or current treatment of CHB Baseline characteristics Characteristic: Entecavir 0.5 mg/d (n=34); Lamivudine 100 mg/d (n=34) Age (yr) mean (SD): 39.8 (10.4); 42.3 (12.6) Sex n (%): 23 (67.6); 28 (82.4)	weeks (n=34) 2 discontinued: 1 for non-compliance and 1 adverse event Also two other doses of entecavir (0.01 and 0.1mg daily; not standard doses so not data extracted)	weeks (n=34) 1 discontinued for adverse event		mean serum HBV DNA - analysis measured by PCR Secondary: reduction of HBV DNA of 2 log10 copies/mL or more or HBV DNA level below the limit of detection (400 copies/mL by PCR assay; 2.5pg/mL or 0.7MEq/mL by bDNA assay); HBeAg loss and seroconversion; normalisation of ALT; drug resistance Adverse events	

male		
HBV DNA (log_{10} copies/ ml)	8.39 (0.73)	7.94 (0.83)
HBeAg positive n (%)	30 (88.2)	31 (91.2)
ALT (IU/L)	142.4 (82.2)	185.0 (130.8)
Genotype: A B C F	 1 (2.94) 1 (2.94) 32 (94.1) 0	 2 (5.88) 2 (5.88) 30 (88.2) 0
Previous interferon	0	0

Effect size (ITT analysis)

	Entecavir 0.5 mg/d (n=32)	Lamivudine 100 mg/d (n=33)	p-value
Outcomes – at week 22			
HBV DNA levels <0.7MEq (2.5pg/mL) by Quantiplex assay n (%)	32/32 (100)	32/33 (97.0)	not reported
Mean (SE) reduction in the serum HBV DNA levels (log_{10} copies/ml)	-5.16 (0.13)	-4.29 (0.18)	p=0.007
HBeAg loss n (%)	1/28 (3.6)	1/30 (3.3)	NS
Rate of HBeAg seroconversion n %	1/28 (3.6)	1/30 (3.3)	NS
Normalisation of ALT levels n %	24/30 (80.0)	25/32 (78.1)	NS
Genotypic resistance	0	0	
Discontinuation due to adverse event	1 (2.9)	2 (5.9)	not reported

Authors' conclusion: Entecavir is well tolerated and produces a dose-dependent reduction in viral load in nucleoside-naive Japanese patients with CHB. Compared with lamivudine, entecavir 0.5mg was superior in this population.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yao 2007	RCT (phase III) Randomisation was performed centrally and stratified by HBeAg status and investigative site. Double blind Target sample size 225 per group to provide 90% power to demonstrate superiority of entecavir over lamivudine (not stated	N= 519	Nucleoside naïve Chinese patients (majority HBeAg positive) Setting: China (26 sites) Inclusion: At least 16 years and had a documented history of chronic HBV infection (HBsAg positive for ≥6 months) and compensated liver disease (total bilirubin ≤2.5mg/dL, INR ≤1.5, albumin ≥3.0g/dL, no current evidence or history of variceal bleeding, hepatic encephalopathy, or ascites requiring diuretics or paracentesis). Eligible patients also had a HBVDNA ≥3 MEq/ml by branched chain DNA assay at screening and evidence of HBV DNA by any commercial assay ≥12 weeks prior to screening, and had ALT 1.3-10 x ULN and at least once ≥12 months prior to screening. Exclusion: Co-infection with HCV, HDV or HIV; other forms of liver disease, more than 12 wk of therapy with nucleos(t)ide analogue with activity against HBV; therapy with any anti-HBV drug within 24 wk prior to randomisation. Patients were not allowed to use traditional Chinese medicine and other herbal medicines intended to improve or protect liver function, or improve or prevent fibrosis, during the study.	Entecavir, 0.5mg/day (n=258) HBeAg (+): n=225 HBeAg (-): n=33 Total duration of treatment: 52 weeks and continue up to 96 weeks if complete response was not achieved at week 48 Loss to follow up: 0;	Lamivudine, 100mg/day (n=261) HBeAg (+): n=221 HBeAg (-): n=40 Total duration of treatment: 52 weeks and continue up to 96 weeks if complete response was not achieved at week 48 Loss to follow up: 4;	Week 48 of treatment	Primary: HBV DNA <0.7MEq/mL (lower limit of detection) by bDNA assay and ALT <1.25 x ULN. Secondary: Log reduction of HBV DNA by PCR assay % with undetectable HBV DNA (<300 copies/ml); % with HBeAg loss and/or seroconversion; % with ALT normalisation (≤1 x ULN)	None reported

	what comparison was)		Baseline characteristics ETV (n=258) / LAM (n=261) Mean age (SD): 30 (9) / 30 (9) HBeAg (+) (%): 225 (87) / 221 (85) Male (%): 211 (82) / 217 (83) Mean serum HBV DNA by PCR (SD), log_{10} copies/ml Overall: 8.64 (0.99) / 8.48 (1.12) HBeAg (+): 8.77 (0.86) / 8.65 (1.0) HBeAg (-): 7.70 (1.28) / 7.59 (1.33) Mean serum ALT (SD), U/L Overall: 196 (140) / 198 (180) HBeAg (+): 191 (135) / 204 (192) HBeAg (-): 225 (169) / 164 (83) Prior IFN-alpha treatment (%): 37 (14) / 42 (16)	4 discontinued (withdrew consent); 1 adverse event; 2 other reasons	0 withdrew consent; 3 adverse event; 6 other reasons		Response to therapy was initially assessed at week 52, based on results obtained at wee k 48. Adverse events	

Effect size * (No reporting of any intention to treat analysis, but data reporting suggests ITT was done.)

HBeAg (+) patients

HBeAg (+) patients Week 48 (treatment duration: 52 weeks)	ETV (0.5 mg/day) (n=225)	LAM (100 mg/day) (n=221)
Mean Log reduction of HBV DNA, log 10 copies/ml (SE)	-6.00 (0.072)	-4.3 (0.134)
% with undetectable HBV DNA (<300	166/225	83/221

copies/ml) (%)		
Incidence of resistance	Not reported	Not reported
% with ALT normalisation (≤1 x ULN)	200 (89)	172 (78)
% with HBeAg loss and/or seroconversion	41 (18)	44 (20)
% with HBeAg seroconversion	33 (15)	39 (18)
% with HBsAg loss and/o≤1 x ULN)r seroconversion	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported
% withdrawn due to adverse events (overall, HBeAg (+) and (-)) (%)	1 (<1)	3 (1)

HBeAg (-) patients

HBeAg (-) patients Week 48 (treatment duration (52 weeks)	ETV (0.5 mg/day) (n=33)	LAM (100 mg/day) (n=40)
Mean Log reduction of HBV DNA, log 10 copies/ml (SE)	-5.22 (0.23)	-4.5 (0.282)
% with undetectable HBV DNA (<300 copies/ml) (%)	31/33	29/40
Incidence of resistance	Not reported	Not reported
% with ALT normalisation	31 (94)	31 (78)
% with HBsAg loss and/or seroconversion	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported
% withdrawn due to adverse events (overall, HBeAg (+) and (-))	1 (<1)	3 (1)

*For all analyses with the exception of mean reduction of HBV DNA, patients with a missing value for an endpoint were considered nonresponders for that end point.

Authors' conclusion: For nucleoside naïve Chinese patients with CHB, ETV achieves superior virological and biochemical benefit over lamivudine, with a comparable

safety profile.

Notes: Yao 2008 (Follow up study)

Telbivudine vs entecavir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Suh 2010	RCT Multi centre international study Open label Parallel group No details of randomisation and allocation concealment.	N=44	Adults with HBeAg-positive compensated chronic hepatitis B (CHB) Inclusion: Aged ≥18 years and had HBeAg-positive CHB with a clinically confirmed diagnosis of compensated liver function (a total serum bilirubin level of ≤2.5 mg/dl, a prothrombin time ≤3 secs longer than normal or an international normalised ratio of ≤1.5, a serum albumin level of ≥3g/dl, and no history of variceal bleeding or hepatic encephalopathy). Eligible patients also had detectable hepatitis B surface antigen (HBsAg) for ≥24 weeks prior to screening. Other inclusion criteria at screening were serum HBV DNA levels of ≥7 log $_{10}$ copies/ml, as determined by a Cobas Amplicor DNA-PCR based assay, a serum alanine aminotransferase level 1.3xto 10.0x the upper limit of normal (ULN), and evidence of chronic liver inflammation documented	Telbivudine 600 mg/day for 12 weeks (n=23) All randomised patients completed treatment, and there were no treatment discontinuations.	Entecavir 0.5 mg/day for 12 weeks (n=21) All randomised patients completed treatment, and there were no treatment discontinuations.	Week 12 (end of treatment). .	Mean log reduction of HBV DNA levels Adverse events	Novartis Pharma AG

	ITT used		upon previous liver biopsy within 24 months of the study or by a history of elevated serum ALT levels on ≥2 occasions within a 6 month period. Exclusion: Exclusion criteria included co-infection with hepatitis C virus, hepatitis delta virus, or HIV virus; the use of interferon or other immunomodulatory agents within 12 months of screening or any previous treatment with oral NA agents; and conditions requiring the frequent, chronic, or prolonged use of systemic corticosteroids or hepatotoxic or nephrotoxic medications. Baseline characteristics <table><tr><td></td><td>Telbivudine (n=23)</td><td>Entecavir (n=21)</td></tr><tr><td>Mean age (yr) (mean SD)</td><td>36.2 (9.62)</td><td>33.4 (8.82)</td></tr><tr><td>Male (no) (%)</td><td>18 (78.3)</td><td>12 (57.1)</td></tr><tr><td>Female (no) (%)</td><td>5 (21.7)</td><td>9 (42.9)</td></tr><tr><td>No (%) of patients with Asian and South Korean race and ethnicity</td><td>23 (100)</td><td>21 (100)</td></tr><tr><td>Time since</td><td></td><td></td></tr></table>				

			diagnosis of CHB: Within past 6 months <1 yr but > 6 months ≥1 yrs ago	 0 (0.0) 2 (8.7) 21 (91.3)	 0 (0.0) 1 (4.8) 20 (95.2)					
			Baseline HBV DNA level Mean (SD) log_{10}copies/ mL	10.29 (1.6)	9.72 (1.7)					
			Baseline AL level (IU/litre) Mean (SD)	163.1 (125.2)	170.2 (152.7					

Effect size

Outcomes (from baseline to week 12)	Telbivudine (N=23)	Entecavir (1.5n=21)	p-value
Mean reduction in HBV DNA levels (log_{10}copies/ml) (SD)	6.6 ±1.6	6.5±1.5	Not reported
Mean reduction in ALT (IU/L)	108.0 (147.87)	116.3 (162.81)	

Authors' conclusion:

During the first 12 weeks of treatment, telbivudine and entecavir demonstrated similar antiviral potencies, resulting in a rapid and profound suppression of serum hepatitis B virus DNA and reduction of alanine aminotransferase levels. No differences in the effects of these agents on early viral kinetics were observed. Both medications were well tolerated.

Notes: study also reported mean reduction in ALT and total drug-related adverse events.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Zheng 2010	RCT Parallel group open label Randomisation by random number table. No details of allocation concealment.	N=131	Adult Chinese patients with previously untreated HBeAg-positive HBV. Inclusion: Patients age 18 to 65 years, had HBeAg positive chronic HBV infection and compensated liver disease with a serum ALT value ≥2 times the upper limit of normal (ULN), and had never received treatment with nucleosides or nucleotides for HBV. Patients were required have a serum HBV-DNA concentration ≥6 log 10 copies/ml at screening. Exclusion: Patients were excluded if they had evidences of infection with HIV, or hepatitis C or D viruses. Other exclusion criteria included pregnancy, breast feeding, alcohol abuse, other forms of liver disease, and impaired renal function. In addition, patients with muscular diseases or baseline serum creatinine phosphokinase (CPK) >190 U/L were also excluded. Baseline characteristics Characteristic: Telbivudine (n=65); Entecavir (n=66) Age , mean (SD) yr: 31.6 (8.7); 33.5 (9.1) Male , no (%): 49 (75.4); 42 (63.6) Female, no(%): 16 (24.6); 24 (36.4)	Telbivudine 600 mg once daily for 24 weeks. (n=65) Loss to follow up/ reason: 64 completed 24 weeks of treatment; reason(s): premature discontinuation, left study area	Entecavir 0.5 mg once daily for 24 weeks. (n=66) Loss to follow up/reason: 63 completed 24 weeks of treatment; reason(s): premature discontinuation; left study area	Week 24	Mean log reduction from baseline in serum HBV DNA concentration % patients with continuous detectable serum HBV DNA (≥500 copies/mL) % HBeAg loss % HBeAg seroconversion Normalisation of serum ALT (≤1 x ULN) *All outcomes were assessed at the end of treatment (week 24)	Scientific Research Foundation of Wenzhou, Zhejiang Province, China.

ALT , mean (SD), U/L	167.3 (100.4) 160.3 (89.8)	
HBV DNA, concentration mean (SD), log 10 copies/ml	7.45 (0.69)	7.51 (0.85)

Effect size

Outcomes	Telbivuidne (n=65)	Entecavir (n=66)	p-v
24 weeks			
Reduction in serum HV DNA concentration, mean (SD), log 10 copies/ml	6.00 (2.07)	5.80 (2.16)	0.3
Proportion of patients with continuous detectable HBV DNA concentration (≥500 copies/mL), % (n/N)	32.3 (21/65)	42.4 (28/66)	0.2
ALT normalisation (≤ 1 x ULN), % (n/N)	78.5 51/65)	74.2 (49/66)	0.5
HBeAg loss, % (n/N)	36.9 (24/65)	28.8 (19/66)	0.3
HBeAg seroconversion, % (n/N)	24.6 (16/65)	13.6 (9/66)	0.1
Patients withdrawn due to adverse events	0	0	--

Authors' conclusion:

In this study of ethnic Han Chinese adults with previously untreated HBeAg-positive HBV infection, there were no statistically significant differences in effectiveness or

tolerability between telbivudine 600 mg and entecavir 0.5 mg at the end of 24 weeks of treatment.

Notes: To detect a different of 0.5 log 10 copies/mL in the mean reduction from baseline of serum HBV DNA conc at week 24 between telbivudine treated and entecavir treated groups, with an SD of 1 within each group, a 2-sided sig. level of 0.05, 80% power, and an expected drop out rate of 5%, >=65 patients per treatment group were needed. Study also reported results at 12 weeks (during treatment).

Lamivudine vs Telbivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention/ Comparisons	Length of follow-up	Outcome measures	Source of funding
Lai CL, Leung N, Teo EK, Tong M, Wong F et al. 2005	RCT (phase 2b) Randomisation: Central randomisation scheme (stratified by serum ALT above or below 2.5 x ULN) using an interactive voice response system, with the system linked to the study drug supply vendor for dispensing of blinded study medications to the study sites	N= 104 ITT analysis	HBeAg positive patients International study, with patients from Hong Kong, Singapore, US, Canada and France. Inclusion: male or female; aged 18-65 years; history of CHB, HBsAg seropositive for ≥6 months; HBeAg positive, serum HBV DNA level > 6 log10 copies/mL; ALT 1.3-10 times ULN; Exclusion: prior treatment with anti-HBV nucleosides or nucleotides; interferon treatment within preceding 12 months; co-infection with HIV, Hep C or delta; history or signs of hepatic decompensation; history of pancreatitis; confounding medical problems; history of alcohol/illicit substance abuse within 2 yrs; Hb <11g/dL (men) or <10g/dL (women); platelets <8x10^4 /mm^3; serum creatine level >1.5 mg/dL; bilirubin > 2 mg/dL; albumin <3.4 g/dL; prothrombin time >3 secs despite vitamin K administration. Baseline characteristics: Differences reported as NS. [ ] Lam n=19 | Tel 600 n=22 | Tel 600 + lam n=20	Lamivudine 100mg/day for 52 weeks (n=19) Telbivudine 400mg/day for 52 weeks(n=22)(non-standard dose) Telbivudine 600mg /day for 52 weeks(n=22) Telbivudine 400mg/day + lamivudine 100mg/day for 52 weeks (n=21) (non-standard dose) Telbivudine 600mg/day + lamivudine 100mg/day for 52 weeks (n=20) Loss to follow up/reasons: Of the 107 randomised in total, 3 withdrew before baseline, but group assignment not given. Then, of the 104 who received at least one dose of treatment, 5 discontinued (1 noncompliance, 2 pregnancy, 1 raised creatine kinase, 1 lost to follow up), but again group assignment not given. ITT analysis of the 104 patients	52 weeks of treatment, no follow up	Log reduction of HBV DNA % with undetectable HBV DNA (<200 copies / mL [lower limit of detection]) Incidence of resistance (viral breakthrough; resistance mutations) % with ALT normalisation % with HBeAg loss and/or seroconversion	Idenix Pharmaceuticals Inc

	Double blind		Median age (range)	34(18-61)	40(19-60)	33 (21-53)		receiving at least one dose was done.		% with HBsAg loss and/or seroconversion
			Sex (% men)	74%	82%	100%				
			Median serum HBV DNA (range), log_{10} copies/ml	9.3 (6.6-12.9)	9 (6.3-13.3)	9.7 (6.4-13.2)				
			Median serum ALT (range), U/L	122 (62-309)	130 (61-325)	132 (32-1657)				
			Prior use of interferon alfa (%)	5	0	5				

Effect size at 52 weeks (assessed at week 48) ITT results only given.

NB No variances given for Log reduction of HBV DNA for un-pooled analysis.

Post-treatment	Lamivudine 100mg/day n=19	Telbivudine 600mg/day n=22	Telbivudine 600mg/day + Lamivudine 100mg/day n=20
Log reduction of HBV DNA (mean – no SD given)	4.57	5.49	5.94
Undetectable HBV DNA	6/19 (32%)	not stated	not stated
HBsAg loss	0	0	0

HBsAg seroconversion	0	0	0
% with ALT normalisation	63% (12/19)	82% (18/22)	74% (15/20)

Authors' conclusion: Patients with CHB treated with telbivudine exhibited significantly greater virologic and biochemical responses compared with lamivudine. Results with the combination regimens were similar to those obtained with telbivudine alone.

Notes: Treatment naive population

Sample size calculation reported: it was estimated that with a total of 100 patients (20 per treatment group), the study allowed detection of a 0.33 $\log_{10}$ difference in reduction of HBV DNA levels between treatment types (LAM vs. TEL vs. combination) and detection of a 0.5 $\log_{10}$ difference in reduction of HBV DNA levels between individual treatment groups, with 80% power at a 2-sided sig. level of alpha = 0.05.

Entecavir vs adefovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Zhao 2011A	Meta-analysis All studies randomised controlled with description of withdrawals and drop-outs.	6 studies (1 in English – Leung 2009 - and 5 in Chinese). Leung n=69; open-label treatment; no other outcomes reported	Nucleos(t)ide-naïve Asian patients with chronic hepatitis B. Inclusion: study design: randomised controlled trial Study population: HBeAg positive nucleos(t)ide-naïve Asian patients with chronic hepatitis B Intervention: the doses of entecavir and adefovir were respectively 0.5 mg/d and 10mg/d, with the duration lasting 48 weeks. Exclusion: Non-human studies, co-infection with hepatitis A, C, D, E, Epstein Barr virus, cytomegalovirus or HIV, co-existence of any other liver diseases such	Entecavir 0.5 mg/d for 48 weeks	Adefovir 10mg/d for 48 weeks	48 weeks	Rates of virological response (Defined as attainment of undetectable levels of serum HBV DNA) Rates of biochemical response (defined as normalisation of serum ALT)	None reported

	Total number of patients included not reported. No details on population other than race (age, sex, baseline serum DNA, ALT etc)	in study	as autoimmune hepatitis, alcoholic liver disease, drug hepatitis or Wilson's disease, liver transplantation, past or current hepatocellular carcinomas; abstracts only. Baseline characteristics					HBeAg clearance (defined as HBeAg disappearance) HBeAg seroconversion (defined as anti-HBeAg appearance)	

literature	Patient races	Study design
Ding 2005	Asian	randomised trial with description of withdrawals and drop-outs.
Zhang 2009	Asian	randomised trial with description of withdrawals and drop-outs.
Lueng 2009	88% Asian	randomised trial with description of withdrawals and drop-outs.
Yang 2010	Asian	randomised trial with description of withdrawals and drop-outs.
Zou 2010	Asian	randomised trial with description of withdrawals and drop-outs.
Huang 2010	Asian	randomised trial with description of withdrawals and drop-outs.

Effect size

outcomes- week 48	Entecavir	Adefovir	RR (95% CI), p-value
Virological response – undectable levels of HBV DNA (from analysis of 4 studies)	105/161	54/148	1.73 (95%CI 1.38 to 2.17), p<0.00001; heterogeneity p=0.21, I^2=32.9%
Biochemical response (ALT normalisation; from analysis of 4 studies)	93/131	76/136	1.25 (95%CI 1.06 to 1.49), p=0.009
HBeAg clearance (from analysis of 5 studies)	17/152	21/154	0.77 (95%CI 0.44 to 1.35), p=0.36
HBeAg seroconversion (from analysis of 3 studies)	6/101	8/106	0.74 (0.28 to 1.94), p=0.53

Authors' conclusion:

Enetcavir is superior to adefovir in decreasing serum HBV DNA and normalising ALT but similar with adefovir in clearing HBeAg and encouraging HBeAg seroconversion for the HBeAg-positive nucleos(t)ide-naïve Asian patients with chronic hepatitis B. Adefovir can be still used for first-line therapy in these patients.

E.6.1.3 Monotherapies for HBeAg negative people with CHB

Adefovir vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hadziyannis 2003	RCT Central randomisation was	N=185	Patients with chronic hepatitis B who were negative for hepatitis B e antigen (HBeAg -ve). Setting: Multicentre at 32 sites (in Canada, Greece, Israel, France, Italy, Australia, Taiwan,	Adefovir dipivoxil 10 mg orally once daily	Placebo once daily for 48 weeks.	At week 48 (end of treatment)	Log reduction of serum HBV DNA levels. [serum HBV	Supported by Gilead sciences

	stratified according to five geographic regions. Permuted blocks (with a block size of 6) were used in each stratum. Double blind (ratio ADV vs. placebo = 2:1)		and Singapore) Inclusion: male and female patients 16 to 65 years of age who had HBeAg-negative chronic hepatitis B and compensated liver disease were eligible. Chronic hepatitis was defined by the presence of detectable HBsAg for at least 6 months, undetectable HBeAg, detectable anti-HBe, a serum HBV DNA level of at least 10^5 copies per millilitre, and an alanine aminotransferase level between 1.5 and 15 times the upper limit of the normal range. Patients had to have a total bilirubin level of no more than 2.5 mg per decilitre, a prothrombin time that was no more than one second above the normal range, a serum albumin level that was at least 3g per decilitre, a serum creatinine level of no more than 1.5mg per decilitre and an adequate blood count. Exclusion: Criteria for exclusion included a coexisting serious medical or psychiatric illness; immune globulin, interferon, or other immune or cytokine-based therapies with possible activity against HBV disease within 6 months before screening; organ or bone marrow transplantation; recent treatment with systemic corticosteroids, immunosuppressant or chemotherapeutic agents, a serum alpha-fetoprotein level of at least 50 ng per millilitre; evidence of a hepatic mass; liver disease that was not due to hepatitis B; prior therapy for more than 12 weeks with a nucleoside analogue with activity against HBV; and seropositivity for HIV or hepatitis C or D virus.	for 48 weeks. (n=123)	(n=62*) *One patient who was assigned to receive placebo never received treatment and was excluded from all analyses.		DNA was measured by the Roche Amplicor polymerase-chain reaction (PCR) assay; lower limit of detection 400 copies/nL) % with undetectable HBV DNA (<400 copies/mL) Serum alanine aminotransferase normalisation HBsAg seroconversion Primary: Histologic improvement [defined as a reduction of at least 2 points in the Knodell necroinflammatory score, with no	

			Baseline characteristics <table><tr><th>Characteristic</th><th>Adefovir dipivoxil (n=123)</th><th>Placebo (n=61)</th></tr><tr><td>Age (yr) mean ±SD</td><td>46±9.8</td><td>45±10.4</td></tr><tr><td>Male - no (%)</td><td>102 (83)</td><td>50 (82)</td></tr><tr><td>Alanine amino transferase level –mean ±SD- U/litre</td><td>143.5±125.3</td><td>149±195.2</td></tr><tr><td>White Black Asian</td><td>82 (67) 5 (4) 36 (29)</td><td>40 (66) 1 (2) 20 (33)</td></tr><tr><td>HBV DNA-log copies/ml mean ±SD</td><td>6.9±0.9</td><td>6.9±1.0</td></tr><tr><td>Knodell score (mean±SD) Total Necroinflammatory activityFibrosis</td><td> 9.6±3.3 7.7±2.7 1.9±1.2</td><td> 8.9±3.4 7.1±2.7 1.8±1.1</td></tr><tr><td>Cirrhosis- no (%)</td><td>14 (11)</td><td>6 (10)</td></tr><tr><td>Prior HBV medications – n (%) Interferon Lamivudine Famciclovir</td><td> 48 (39) 10 (8) 7 (6)</td><td> 28 (46) 4 (7) 7 (11)</td></tr></table>			concurrent worsening of the Knodell fibrosis score.	

Effect size

Outcomes- at week 48	Adefovir dipivoxil (n=123)	Placebo (n=61)	p-value
Reduction in serum HBV DNA levels- median	3.91 log copies/ml	1.35 log copies/ml	<0.001
Patients with undetectable HBV DNA (<400 copies/mL)	63/123 (51%)	0/61 (0%)	
Histologic improvement (%)	77/121 (64)	19/57 (33)	p<0.001
Normalised alanine aminotransferase level	84/116 (72%)	17/59 (29%)	<0.001
Mean (SD) change in Knodell scores baseline to week 48 among patients with assessable liver biopsy specimens (adefovir n=112; placebo n=55): total necroinflammatory fibrosis	 -3.7 (3.1) -3.4 (2.9) -0.3 (0.7)	 0.4 (3.7) 0.3 (3.2) 0.1 (0.9)	 <0.001 <0.001 0.005
Resistance	0	0	

Authors' conclusion:

In patients with HBeAg-negative chronic hepatitis B, 48 weeks of adefovir dipivoxil treatment resulted in significant histologic, virologic, and biochemical improvement, with an adverse event profile similar to that of placebo. There was no evidence of the emergence of adefovir-resistant HBV polymerase mutations.

Notes: Treatment naïve and previous treated with IFN-alpha (41% patients)

Lamivudine vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Tassopoulos 1999	Double blind RCT - randomizati	N=125	Inclusion: HBeAg negative patients (at screening and for at least 6 months before); men and women 16-70 years old; with detectable HbsAg and detectable HbeAb for at	Lamivudine 100 mg orally once daily (n=60)	Placebo (n=65 randomised; 64 analysed	26 weeks double blind	Primary: "complete responders": undetectable	Glaxo Wellcome Researc

	on method; adequate (computer generated codes) -allocation concealment: unclear - blinding: double blinded for the first 26 weeks, then unblinded ➔ at week 24 patients were analyzed for DNA➔ based on results: - HBV DNA> 2.5 pg/mL; patients in both groups were withdrawn - HBV DNA< 2.5 pg/mL; in the LAM group continued on treatment and in		least 6 months, HBV DNA concentration ≥2.5 pg/mL at screening and HBV DNA present in serum for at least 3 months before; ALT concentration ≥1.5 and less than 10 times the upper limit of normal (ULN) at screening and at least once ≥3 months before, previously treated with other antiviral drugs but not within 30 days of the start of the trial.Multinational. Exclusion: coinfected with Hepatitis C or D, HIV, decompensated liver disease (bilirubin >2.5 times ULN, prothrombin time prolonged >3s, albumin <3g/dL, history of ascites, variceal hemorrhage or hepatic encephalopathy) or evidence of autoimmune hepatitis (antinuclear antibody titre >1:160). Baseline characteristics [table]	26-week double blind phase; total duration of treatment: up to 52 weeks Loss to follow up/reasons: 53/60 completed 52 weeks (5 withdrawn at week 26 following protocol [i.e. if HBV DNA positive at week 24], 1 due to adverse events, 1 due to protocol violation)	as 1 patient did not have evidence of chronic Hep B) 26-week double blind phase; total duration of treatment: 26 weeks Loss to follow up/reasons: 60/64 completed the 26 weeks; 43/64 withdrawn at week 26 following protocol, 15/64 completed the follow up until 52 weeks.	treatment (plus follow up at week 52 after some patient had stopped and some continued therapy)	HBV DNA (<2.5 pg/mL by Chiron Quantiplex bDNA assay) plus ALT normalisation; "partial responders": HBV DNA <2.5pg/mL but not normal ALT; nonresponders: HBV DNA ≥2.5pg/mL % with HBsAg loss and/or seroconversion Histologic improvement (week 52) Incidence of resistance (genotypic YMDD mutation at week 52) Adverse events	h and Development, Greenford, UK

	Lamivudine (n=60)	Placebo (n=64)
Median age (range)	42 (24-65)	44 (17-63)
Sex (% men)	83%	77%
Median HBV DNA (range), pg/mL	255 (1.3-18000)	95.5 (1.3-3900)
Median serum ALT (range), x ULN	3.2 (0.6-16.4)	3.3 (0.7-12.5)
n (%) of patients with HBeAg (negative)	63 (98%)	59 (98%)
Number (%) of patients with evidence of	8 (14%)	10 (18%)

	placebo stopped treatment and followed up		cirrhosis					

Effect size (of the 54 patients in each group with elevated ALT and HBV DNA ≥2.5pg/mL at baseline)

Post-treatment (end of week 24)	Lamivudine (100mg/day) (n=54)	Placebo (n=54)	p value
Complete responders: undetectable HBV DNA (<2.5 pg/mL) plus ALT normalisation	34/54 (63%)	3/54 (6%)	p<0.001
Partial responders: undetectable HBV DNA (<2.5 pg/mL) without ALT normalisation	15/54 (28%)	11/54 (20%)	
Total undetectable HBV DNA (<2.5pg/mL)	49/54 (91%)	14/54 (26%)	
Log reduction of HBV DNA	Not reported	Not reported	--
% with ALT normalisation	Not reported	Not reported	--
% with HBeAg loss and/or seroconversion	Not reported	Not reported	--
% with HBsAg loss	0%	1/54	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	--
% withdrawn due to adverse events	1/54	1/54	

Notes: Sample size calculation - yes; the study was powered to detect a difference in complete response between lamivudine and placebo; the planned sample size of 102 patients provided 80% power to detect a 20% difference (considered to be the mimimum clinically relevant difference) in complete response (HBV DNA loss plus ALT normalization).

Authors' conclusion: Lamivudine treatment results in a significant virological and biochemical improvement compared with placebo, indces an improvement or no change in histology in most paitns and is well tolerated The response to lamivudine therapy in HBeAg-negative patients is similar to teh response reported in previous studies of patiens with HBeAg-positive chronic hepatitis B.

Reference	Study type	Number of	Patient characteristics	Intervention	Comparison	Length of	Outcome measures	Source of

<table>
<tr><th></th><th></th><th>patients</th><th></th><th></th><th></th><th>follow-up</th><th></th><th>funding</th></tr>
<tr>
<td>Chan 2007c; Two-year lamivudine treatment for hepatitis B e antigen-negative chronic hepatitis B: a double-blind, placebo-controlled trial</td>
<td>Multicentre, double blind, placebo-controlled RCT

- randomization method; centralized and stratified by geographical region
- blinding: double blind
-allocation concealment: not stated</td>
<td>N=139</td>
<td>Inclusion: HBeAg-negative (for at least 6 months prior to study) treatment naïve patients (over 18 years old) with chronic hepatitis B (positive for HBsAg for at least 6 months), HBV DNA detectable by a non-PCR based assay or >100,000 copies/mL by TaqMan real-time PCR assay, significantly increased ALT (1.5-10 x ULN on ≥2 occasions within previous 6 months and at screening, or ALT above ULN with ≥1 biochemical flare-up [ALT >200IU/L] in past 12 months); liver biopsy within 12 months showing evidence of active hepatitis.
8 sites in Hong Kong and China.
Exclusion: hepatocellular carcinoma, ALT > 10 x ULN, decompensated liver disease, complications of liver cirrhosis, coinfection with hepatitis C or D or HIV, serious medical or psychiatric illnesses, use of immunosuppressive or immunomodulatory therapy within the last 6 months, treatment with antiviral agent in last 6 months, history of hypersensitivity to nucleoside analogues, serum creatinine >1.5 x ULN, antinuclear antibody titre >1:160, serum amylase or lipase level >2 x ULN, Hb <11g/dL, white cell count <3 x 10^9/L, platelet count <100 x 10^9/L, pregnant or lactating women.

Baseline characteristics
<table>
<tr><th></th><th>Lamivudine (n=89)</th><th>Placebo (n=47)</th></tr>
<tr><td>Median age (range)</td><td>40 (18-58)</td><td>41 (17-63)</td></tr>
<tr><td>Median BMI (range), kg/m2</td><td>23.0 (16.3-39.8)</td><td>23.8 (18.8-30.1)</td></tr>
</table>
</td>
<td>Lamivudine (100mg/day) (n=89)

Total duration of treatment: 24 months

Loss to follow up/reasons: 16 drop outs and 4 with data missing until the end of treatment, another 15 drop outs and 1 with data missing untile the end of 6 months follow up</td>
<td>Placebo (n=47)

Total duration of treatment: 24 months

Loss to follow up/reasons: 9 drop outs and 3 with data missing until the end of treatment, another 4 drop outs and 1 with data missing untile the end of 6 months follow up</td>
<td>24 months of treatment plus 6 months follow up</td>
<td>Primary: “Complete response”: HBV DNA undetectable (either by NAXCOR cross-linking assay, limit of detection 0.5MEq/mL or HBV DNA <10,000 copies/mL by PCR-based assay) plus ALT normalisation at month 24

% with undetectable HBV DNA (<10,000 copies/ml, by TaqMan real time PCR assay)

Incidence of resistance (genotypic and phenotypic)</td>
<td>GlaxoSmithKline</td>
</tr>
</table>

Sex (% men)	75 (84%)	39 (83%)
Median serum HBV DNA (range), log_{10} copies/ml	6.1 (2.0-8.4)	5.8 (2.0-8.0)
Median serum ALT x ULN (range)	1.6 (0.2-11.4)	1.8 (0.4-13.0)
HBeAg negative n (%)	84 (94%)	44 (94%)
Cirrhosis n (%)	16 (31)	6 (21)
HBV genotype n (%): negative	3 (3)	0 (0)
B	32 (36)	12 (26)
B+C	2 (2)	3 (6)
C	51 (57)	31 (66)
D	1 (1)	1 (2)

% with ALT normalisation

% with HBsAg loss

Histologic improvement (≥2 points improvement in necroinflammatory and fibrosis scores)

Adverse events

Effect size

Week 24	Lamivudine (100mg/day) (n=70)	Placebo (n=35)	Differene between groups
Complete response (undetectable HBV DNA and ALT normalisation) n (%)	50 (56% of originally randomised 89 patients)	5 (11% of originally randomised 47 patients)	Absolute difference 46%, 95% CI 30-55%, p<0.001; after adjustment for baseline HBV DNA and ALT levels, OR: 10.8, 95% CI 3.8-30.2, p<0.001
Median log reduction of HBV DNA (range)	3.21 log copies/ml (-3.96 to +6.36)	0.47 log copies/ml (-4.85 to +4.91)	Absolute difference: 2.21 (95% CI 1.19 to 3.28), P<0.001
% with undetectable HBV DNA	52 (58% of 89)	9 (19% of 47)	Absolute difference 39%, 95% CI 22-52%, p<0.0001
% with ALT normalisation	66 (74% of 89)	17 (36% of 47)	Absolute difference 38%, 95% CI 22-55%, p<0.001)
% with HBeAg loss and/or seroconversion	Not reported	Not reported	--
% with HBsAg loss and/or seroconversion	0	0	--
Quality of life measures (EQ-5, SF-35, liver	Not reported	Not reported	--

disease specific)			
Histologic improvement*	14/18 with paired biopsy data (78%)	2/8 with paired biopsy data (25%)	Absolute difference 53%, 95% CI 12-77%, p=0.034
% withdrawn due to adverse events	Not reported	Not reported	
Genotypic resistance (detection of mutations)	22/70 (31)	1/35	Not stated
Phenotypic resistance (≥1 log increased HBV DNA from previous levels)	16/70 (23)	0/35	Notstated

Follow up (6 months)	Lamivudine (100mg/day) (n=54)	Placebo (n=30)	Difference between groups
Log reduction of HBV DNA	Not reported	Not reported	
% with undetectable HBV DNA	29 (33% of original 89 patients)	12 (26% of original 47)	Absolute difference 7%, 95% CI -9 to +21, p=0.39
% with ALT normalisation	53 (60% of 89)	18 (38% of 47)	Absolute difference 21%, 95% CI 4-39, p=0.02
% with HBeAg loss and/or seroconversion	Not reported	Not reported	
% with HBsAg loss	1/54	0/30	
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	
% withdrawn due to adverse events	Not reported		

*The second liver biopsy was an optional examination and 26 patients had paired biopsy. Unclear when the second liver biopsy was done.

Notes: -HCC was detected in 3 patients in lamivudine group and 1 patient in placebo group.

Authors' conclusion: Two-year lamivudine treatment was effective in HBeAg-negative chronic hepatitis B. However, the response is not sustained after treatment cessation.

Interferon vs. Lamivudine; lamivudine + interferon versus lamivudine; lamivudine + interferon versus interferon

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Schalm SW, Heathcote J, Cianciara J, Farrell G, Sherman M, Willems B, Dhillon A, Moorat A, Barber J, Gray DF. 2000	RCT-double blinded (for the lamivudine group, double blinded until week 8, single blinded from 8-52 weeks; other groups remained blinded) - Computer generated randomisation sequence but incomplete allocation concealment. Results of HBV serology kept blinded during treatment and follow up.	N= 230 randomised; 226 analysed as ITT population	Inclusion: male and female; 16-70 years; detectable HBsAg and HBeAg in serum at time of screening and for at least 6 and 3 months respectively before study entry; serum HBV DNA levels of at least 5 pg/ml at screening; inflammation shown by histology or raised ALT (1.3 – 10 x ULN) at screening and at least 3 months prior to screening. Setting: Multicenter (51 centres in 15 countries). Exclusion: Previous treatment with interferon or had received antiviral therapy in last 6 months; co-infection with Hep C, D or HIV; decompensated liver disease (serum bilirubin >2.5 x ULN, prothrombin time prolonged >3s, albumin < lower limit of normal, history of ascites, variceal haemorrhage or hepatic encephalopathy); liver disease of other aetiology; contraindications to interferon. Baseline characteristics. Described as well matched. | | Lam + IFN (n=75) | IFN (n=69) | Lam (n=82) | | | | | |	Combination therapy: lamivudine 100mg daily for 8 weeks then 16 weeks of lamivudine 100mg daily + interferon α 10 million units three times weekly subcutaneously (n=75; 2 withdrawn for AE, 5 lost to follow up, 6 other withdrawal, n=62 at week 52, 1 more lost to follow up by week 64, n=61) Interferon monotherapy group:		All patients followed to week 64: 52 weeks of treatment + 12 weeks follow up for the lamivudine monotherapy group and 24 weeks treatmetn + 40 weeks follow up for other 2 groups	Primary: HBeAg seroconversion and HBeAg loss and undetectable HBV DNA at week 52 Secondary: Histological response (≥2 point reduction in HAI at week 52), HBV DNA loss (solution hybridisation assay, lower limit of detection 3pg/mL) at week 52 and ALT normalisation at week 52	Glaxo Wellcome

			Median (range) age	31 (15-60)	32 (16-70)	30 (16-69)	Placebo once daily for 8 weeks, then placebo once daily plus interferon (10^7 units subcutaneously 3 x weekly) for 16 weeks. (n=69; 9 were lost prior to 52 weeks (0 due to adverse events; 5 lost to follow up, 4 other reasons) so n=60 at week 52 and a further 2 lost to follow up prior to week 64; final n=58)			Incidence of resistance (YMDD mutation) at week 52 and week 64 Adverse events	
			% Male	71	81	71					
			Median (range) wt (kg)	72 (42-115)	71 (45-115)	68.5 (45-118)					
			Caucasian % Asian-Oriental %	59 31	65 28	65 29					
			Mean (SD) ALT (x ULN)	3.2 (3.4)	3.1 (2.1)	3.3 (2.8)					
			Median (range) ALT	2.2 (0.8-26.1)	2.4 (0.8-10.1)	2.6 (0.8-19.2)					
			ALT <1 x ULN n (%)	4 (5)	3 (4)	4 (5)					
			Mean $\log_{10}$ (SD) HBV DNA (pg/ml)	1.74 (0.75)	1.78 (0.77)	2.04 (0.66)					
			Median (range) HBV DNA (pg/ml)	94.0 (1.5-786)	109.0 (1.5-1322)	136.0 (1.5-2264)					
			HBV DNA <3 pg/ml n (%)	4 (5)	9 (13)	2 (2)					
			HBeAg	72	68	81 (99)					

			+ve n (%)	(96)	(99)				
			HBV DNA and HBeAg +ve n(%)	68 (91)	64 (93)	80 (98)			
			Median (range) Knodell HAI score	4 (0-14)	4 (0-13)	4 (0-12)			
			HAI <2 n (%)	8 (11)	6 (9)	11 (5)			
			Cirrhosis n (%)	3 (4)	8 (12)	5 (6)			

Results:

Outcome	LAM + IFN (n=68)	IFN (n=64)	Lam (n=80)	Combination vs. IFN	Combination vs. Lam
% of patients with HBeAg seroconversion at week 52	20/68 (29%)	12/64 (19%)	14/80 (18%)	OR 1.9 (95% CI 0.8 to 4.4), p=0.12	OR 2.0 (0.9 to 4.7), p=0.10
% of patients with HBeAg seroconversion at week 64	17/68 (25%)	14/64 (22%)	16/80 (20%)	not stated	not stated
Histological response (≥2 point reduction in HAI) at wek 52	21/57 (37%)	25/54 (46%)	31/63 (49%)	not stated	not stated
% of patients with HBeAg loss (52 weeks)	19/55 (35%)	13/56 (23%)	14/60 (23%)	not stated	not stated
% of patients with HBeAg loss (64 weeks)	18/55 (33%)	14/48 (29%)	13/62 (21%)	not stated	not stated
% of patients with undetectable HBV DNA (< 3 pg/ml = approx 8 x 10^6 copies/ml) at 52 weeks	20/55 (36%)	16/55 (29%)	36/60 (60%)	not stated	not stated
% of patients with undetectable HBV DNA (< 3 pg/ml) at 64 weeks	17/55 (31%)	14/49 (29%)	20/63 (32%)	not stated	not stated
% of patients with ALT normalisation (<1xULN) at 52 weeks	21/55 (38%)	16/55 (29%)	33/58 (57%)	not stated	not stated

% of patients with ALT normalisation (<1xULN) at 64 weeks	18/50 (36%)	16/50 (32%)	13/63 (21%)	not stated	not stated
Incidence of YMDD variant HBV 52 weeks Incidence of YMDD variant HBV 64 weeks	0 0	0 0	19/61 (31%) 12/57 (21%)	not stated	not stated
Patients with adverse events leading to withdrawal	2	0	3	not stated	not stated

Notes: sample size calculation: Based on an estimated HBeAg seroconversion rate of 40% for interferon and lamivudine monotherapy and 65% for combination therapy, sample size of 210 patients had 80% powerto detect a significant difference in seroconversion rates between combination therapy and either of the two monotherapies (not powered for comparison between the monotherapies).

Interferon treatment naive

Duration: 52 weeks for LMV monotherapy, 24 for other treatments

No co-infections

Setting: International multicentre study.

Adverse events were more common in the combination and interferon groups than the lamivusdine monotherapy group.

Authors' conclusion: HBeAg seroconversion rates at one year were similar for lamivudine monotherapy and a standard course of interferon. Combination therapy may be more effective than either monotherapy.

Telbivudine vs. lamivudine – POSITIVE AND NEGATIVE

Reference	Study type	No.	Patient characteristics	Interventio	Comparison	Leng	Outcome	Source

		patients		n		th of follow-up	measures	of funding
Lai 2007 (same study as Liaw 2009)	RCT Double blind. Treatment assignments were according to HBeAg status (positive or negative) and a serum alanine aminotransferase level >2.5 or ≤2.5 times the upper limit of normal. Within each stratum patients were randomly assigned in block sizes of four.	N= 1370 (921 HBeAG positive and 446 HBeAg negative)	HBeAg positive and negative patients Inclusion: Men and women between 16 and 70 years of age who had HBeAg positive or HBeAg-negative chronic hepatitis B were eligible to participate in the study. Chronic hepatitis was defined by detectable serum hepatitis B surface antigen, serum alanine aminotransferase level 1.3 to 10 times the upper limit of normal, a serum HBV DNA level greater than 6 log 10 copies per millilitre, and compatible pre-treatment liver histologic findings. Exclusion: Co-infection hepatitis C, hepatitis D, or the HIV virus; evidence of hepatic decompensation, pancreatitis, or hepatocellular carcinoma; previous treatment for hepatitis B with nucleoside or nucleotide analogues or both; treatment with interferon or other immunomodulators within the previous 12 months; other forms of liver disease; a serum creatinine level greater than 1.5 mg per decilitre; a serum amylase or lipase level greater than 1.5 times the upper limit of normal ; a prothrombin time prolonged by more than 3 seconds; a serum albumin level less than 3.3 g per decilitre; and a bilirubin level greater than 2.0 mg per decilitre. Eligible patients with a serum alpha fetoprotein level greater than 50 ng per millilitre required exclusion of underlying hepatocellular carcinoma. Baseline characteristics <table><tr><td></td><td>HBe Ag-positiv</td><td>HBe Ag-positiv</td><td>HBe Ag-negat</td><td>HBe Ag-negative lamivudin</td></tr></table>	600 mg of telbivudine once daily n=458 HBeAg (+) n=222 HBeAg (-) 18 patients withdrew before week 52, of which 2 discontinued treatment because of adverse events, clinical disease progression or lack of efficacy.	100 mg of lamivudine once daily n=463 HBeAg (+) n=224 HBeAg (-) 32 patients withdrew before week 52, of which 8 discontinued treatment because of adverse events, clinical disease progression or lack of efficacy.	Week 52	Change in the serum HBV DNA level Patients with undetectable HBV DNA by PCR (lower limit of detection 300 copies/mL) HBeAg and HBsAg loss and seroconversion. Normalisation of serum ALT level. Incidence of	Idenix pharmaceuticals and Novartis pharmaceuticals

			e Telbivudine (n=458)	e (n=463)	ive Telbivudine (n=222)	e (n=224)				resistance (viral breakthrough with treatment emerging resistance mutation) Histologic improvement
			Age (yrs) mean (range)	32 (16-63)	33 (16-67)	43 (17-68)	43 (18-68)			
			Male- no (%)	333 (73)	351 (76)	174 (78)	177 (79)			
			Serum alanine aminotransferase level – IU/litre (mean)	146.4±5.37	158.9±6.30	137.0±6.94	143.7±8.74			
			Serum HBV DNA –log 10 copies/ml (mean)	9.5±0.09	9.5±0.09	7.7±0.12	7.4±0.10			
			Mean total Knodell histologic activity index score	8.9	9.0	9.0	9.6			
			Mean Knodell necroinflammatory score	7.4	7.3	7.3	7.6			
			Mean Ishak fibrosis	2.1	2.2	2.3	2.5			

			score								
			Chinese non-Chinese Asian White Black Latino Middle Easter/Indian Other	265 (57.9) 115 (25.1) 52 (11.4) 4 (0.9) 2 (0.4) 8 (1.7) 12 (2.6)	265 (57.2) 106 (22.9) 55 (11.9) 7 (1.5) 4 (0.9) 7 (1.5) 19 (4.1)	116 (52.3) 29 (13.1) 46 (20.7) 3 (1.4) 2 (0.9) 6 (2.7) 20 (9.0)	102 (45.5) 42 (18.8) 56 (25.0) 3 (1.3) 4 (1.8) 4 (1.8) 13 (5.8)					

Effect size

Outcomes- at week 52	HBe Ag-positive Telbivudine (n=458)	HBe Ag-positive Lamivudine (n=463)	Difference (95% CI)	p-value	HBe Ag-negative Telbivudine (n=222)	HBe Ag-negative lamivudine (n=224)	Difference (95% CI)	p-value
Serum HBV DNA level (mean change log 10 copies/ml from baseline	-6.45	-5.54	-0.91 (-1.20 to -0.61)	<0.001	-5.23	-4.40	-0.83 (-1.20 to -0.45)	<0.001
Patients with undetectable HBV DNA by PCR (%)	60% (275/458)	40.4% (187/463)		<0.001	88.3% (196/222)	71.4% (160/224)	16.9 (9.6 to 24.1)	<0.001
ALT normalisation (%)	354 (77.2)	347 (74.9)	2.3 (-3.3 to 7.9)	0.42	165 (74.4)	178 (79.3)	-4.9 (-13.0 to 3.2)	0.24

HBeAg loss (%)	118 (25.7)	108 (23.3)	2.4 (-3.2 to 8.1)	0.40	-	-	-	-
HBeAg seroconversion (%)	103 (22.5)	100 (21.5)	1.0 (-4.5 to 6.4)	0.73	-	-	-	-
Histologic response (%)	296 (64.7)	261 (56.3)	8.4 (2.0 to 14.7)	0.01	148 (66.6)	148 (66.0)	0.6 (-8.3 to 9.5)	0.90
Incidence of resistance (%)	23 (5)	51 (11)	-6.0 (-9.5 to -2.5)	<0.001	5 (2.2)	24 (10.7)	-8.5 (-12.9 to -4.0)	<0.001

Authors' conclusion:

Among patients with HBeAg positive chronic hepatitis B, the rates of therapeutic and histologic response at 1 year were significantly higher in patients treated with telbivudine than in patients treated with lamivudine. In both HBeAg-negative and the HBeAg –positive groups, telbivudine demonstrated greater HBV DNA suppression with less resistance than did lamivudine.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

<table>
<tr>
<td>Liaw YF, Gane E, Leung N et al. 2009

Same study as Lai 2007</td>
<td>RCT
Double blind phase 3 trial
Computer generated randomisation, via central telephone (which suggests allocation concealment).
Analysis stratified according to +ve or –ve HBeAg status and serum ALT level (> or < 2.5 times the ULN).</td>
<td>1370 patients

ITT analysis
All discontinued patients were imputed using “last observation carried forward” for continuous variables or treated missing dichotomous data as a failure.</td>
<td>HBeAg positive and negative patients
Inclusion: 16-70 yrs; HBeAg +ve or –ve CHB; compensated liver disease; serum ALT level 1.3-10 x ULN; serum HBV DNA level >6 log10 copies/mL
Setting: 112 centres in 20 countries.
Exclusion: prior Rx with anti HBV nucleosides or nucleotides.

Baseline characteristics. Reported as well-matched.
<table>
<tr><td></td><td colspan="2">HBeAg +ve</td><td colspan="2">HBeAg -ve</td></tr>
<tr><td></td><td>TBV</td><td>LMV</td><td>TBV</td><td>LMV</td></tr>
<tr><td>n</td><td>458</td><td>463</td><td>222</td><td>224</td></tr>
<tr><td>Mean age (range)</td><td>32(16-63)</td><td>33(16-67</td><td>43(17-68)</td><td>43(18-68)</td></tr>
<tr><td>Male%</td><td>73</td><td>76</td><td>78</td><td>79</td></tr>
<tr><td>Mean wt (range)</td><td>66(38-126)</td><td>68(38-150)</td><td>72(42-123)</td><td>71(45-148)</td></tr>
<tr><td>Chinese(%)</td><td>58</td><td>57</td><td>52</td><td>46</td></tr>
<tr><td>HBV genotype (n)
A
B
C
D
OTHER</td><td>
24
129
259
42
3</td><td>
31
113
258
54
7</td><td>
12
59
89
57
5</td><td>
14
59
86
64
1</td></tr>
<tr><td>Serum ALT (IU/L) mean (se)</td><td>146.2 (5.4)</td><td>158.9 (6.3)</td><td>137(6.9)</td><td>143.7 (8.7)</td></tr>
<tr><td>Serum ALT level > 2 x ULN (n)</td><td>295</td><td>293</td><td>130</td><td>125</td></tr>
<tr><td>Serum HBV DNA level (log10copies/mL) mean (se)</td><td>9.5(0.1)</td><td>9.5(0.1)</td><td>7.7(0.1)</td><td>7.4(0.1)</td></tr>
</table>
</td>
<td>Telbividine (TBV) 600mg once daily AND dummy lamivudine (LMV).
N=683
HBeAg (+) = 45
HBeAg (-) = 222
2 year treatment duration (104 weeks)
Loss to follow up:
Immediate loss of 3 prior to baseline measures from TBV group. At week 104, further loss of 56 (non compliance 8, adverse events 5, lack of efficacy 6, patient/investigator request 33, pregnancy 4)</td>
<td>Lamivudine 100mg once daily AND dummy TBV.
N=687
HBeAg (+) = 463
HBeAg (-) = 224
2 year treatment duration.
(104 weeks)
Loss to follow up:
At week 104, 88 lost to F/U (non compliance 6, adverse events 10, clinical disease progression 2, lack of efficacy 16, death 1, patient/investigator request 48, pregnancy 1).</td>
<td>104 weeks. Primary analysis at 52 weeks.</td>
<td>Serum HBV DNA changes from baseline.

% patients with HBV DNA non detectable by PCR assay (≥300 copies/mL)

HBeAg loss and seroconversion

Normalisation of serum ALT level

Hep B surface antigen (HBsAg) loss and seroconversion.

Incidence of resistance (viral resistance, defined as viral breakthrough with the emergence of a treatment</td>
<td>not stated</td>
</tr>
</table>

Results: %s given. All ITT.

	HBeAg +ve		p	HBeAg -ve	
Outcome	TBV (n=458)	LMV (n=463)		TBV (n=222)	LMV (n=224)
Patients with undetectable HBV DNA by PCR assay (<300 copies/mL). Week 104	255 (55.6)	178 (38.5)	<0.001	182 (82)	127 (56.7)
HBV DNA <5 log 10 week 104	78.4%(359/458)	61.5%(285/463)	<0.0001	93.3%(207 /222)	86.8%(194 /224)
ALT normalisation week 104	69.5%(318/458)	61.7%(286/463)	<0.05	77.8%(173/222)	70.1%(157/224)
HBeAg loss week 104	35.2%(161 /458)	29.2%(135 /463)	0.056	NA	NA
HBeAg seroconversion week 104	29.6%(136/458)	24.7%(114 /463)	0.095	NA	NA
HBsAg loss week 104	1.3%(6 /458)	1.3%(6/463)	0.993	0.5%(1 /222)	0.9%(2/224)
HBsAg seroconversion week 104	0.4%(2/458)	0.7%(3 /463)	0.661	0.5%(1/222)	0.4%(1/224)
Viral resistance week 104	25.1%(115/458)	39.5%(183/463)	<0.001	10.8%(24/222)	25.9%(58/224)
Adverse events leading to discontinuation: 10 in LMV group and 5 in TBV group (overall – HBeAg positive and negative)					

NOTES:
Nucleoside NAIVE
Duration: 104 weeks
No co-infections
Setting: International multicentre study.
Predominant genotype: not stated

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hou 2008A	Randomised phase III	N=332 (290	Patients with compensated hepatitis B e antigen (HBeAg)-positive or HBeAg-negative chronic	600 mg of telbivudine	100 mg lamivudine	No follow up.	Mean reduction in	Idenix Pharmac

	trial Multi centre. Centralised randomisation. At randomisation patients were stratified by HBeAg status (positive or negative) and serum alanine aminotransferase (ALT) level[<2.5 or ≥2.5 times the upper limit of normal] Double blind. Study powered for treatment differences	HBeAg + and 42 HBeAg -)	hepatitis B. Inclusion: Eligible patients were Chinese males or females, 16 to 70 years of age, with a clinical history compatible with chronic hepatitis B and active viral replication, documented by positive serum HBsAg, HBeAg-positive or HBeAg-negative, serum HBV DNA ≥6 log $_{10}$ copies/ml, serum ALT levels ≥1.3 times upper normal limit but <10 times upper normal limit at the screening visit, and a liver biopsy compatible with chronic hepatitis B obtained within 12 months prior to randomisation. Exclusion: History of evidence of decompensated liver disease; pregnancy or breast feeding, unwillingness to use a double barrier method of contraception; co-infection with hepatitis C virus, hepatitis D virus, or HIV virus; previous treatment for HBV wit nucleoside analogues; treatment with interferon or other immunomodulators in the 12 months prior to screening; abuse of alcohol or illicit drugs within the past 2 years; frequent or prolonged use of systemic corticosteroids, acyclovir or famciclovir; hepatocellular carcinoma or other malignancy requiring treatment; other serious medical conditions that might confound efficacy or safety assessments; use of anticoagulants; and a history of clinical pancreatitis. Laboratory exclusion criteria included haemoglobin <11g/dl for men and <10g/dl for women; neutrophil count <1500/mm^3; platelet count <75,000/mm^3; serum creatinine ≥1.5 mg/dl; serum amylase and lipase levels ≥1.5 times upper normal limit; serum albumin <3.3 g/dl; prothrombin time prolonged by >3 seconds over the upper limit of	once daily for 104 weeks n=167 147 HBeAg (+) 22 HBeAg (-) 4 patients in the telbivudine withdrew from the study before week 52, of which one (0.6%) was discontinued for adverse events, clinical disease progression or lack of efficacy.	once daily for 104 weeks n=165 143 HBeAg (+) 22 HBeAg (-) 5 in the lamivudine group withdrew from the study before week 52, of which one (0.6%) was discontinued for adverse events, clinical disease progression or lack of efficacy.	Outcomes were measured at 52 weeks	serum HBV DNA at week 52 of treatment. Proportions of patients with serum HBV DNA reduction to < 5 log $_{10}$ copies/ml on 2 successive visits. % patients with detectable HBV DNA ALT normalisation HBeAg loss and seroconversion Incidence of resistance (viral breakthrough with treatment	euticals and Novartis Pharmaceuticals

	on primary endpoint at 1 year (HBV DNA reduction) in the overall (HBeAG + and -) population; adequately powered for HBeAg subgroup only (but not for much smaller HBeAg negative subgroup)		the reference value; and total bilirubin ≥2.0 mg/dl. Patients with serum alpha-fetoprotein >50ng/mL required exclusion of underlying hepatocellular carcinoma prior to randomisation. Baseline characteristics Characteristic: HBeAg positive Telbivudine (n=147); HBeAg positive Lamivudine (n=143); HBeAg Negative Telbivudine (n=20); HBeAg Negative Lamivudine (n=22) Age mean range (yrs): 28 (16-64); 29 (15-63); 38 (20-56); 36 (19-58) Gender -male (%): 80; 75; 85; 86 HBV DNA: mean log10 copies/ml (SE): 9.3 (0.123); 9.7 (0.133); 7.8 (0.389); 7.6 (0.346) ALT: mean IU/l (SE): 156 (9.6); 157 (12.6); 162 (23.9); 177 (75.2) Genotype (%): C: 60; 64; 65; 82 B: 40; 36; 30; 18				emerging resistance mutation)	

Effect size

Outcomes - HBeAg positive patients	Telbivudine (n=147)	Lamivudine (n=143)	Difference (95% CI)	p-value
Serum HBV DNA (mean log $_{10}$ reduction from baseline)	-6.3	-5.5	-0.84 (-1.3 to -0.4)	<0.001
Patients with undetectable HBV DNA by PCR assay (%)	98/147 (67)	54/143 (38)	29 (18.0 to 39.8)	<0.001
ALT normalisation (%)	128 (87)	107 (75)	12.6 (3.5 to 21.7)	0.007
HBeAg loss (%)	46 (31)	29 (20)	10.2 (0.1 to 20.3)	0.047
HBeAg seroconversion (%)	37 (25)	26 (18)	7.3 (-2.3 to 16.9)	0.14
Viral breakthrough n (%)	11 (7.5)	20 (17.5)	-10.0 (-17.5 to -2.5)	0.009
Viral resistance	11 (7.5)	21 (14.7)	-7.2 (-14.4 to 0)	0.06
HBsAg loss	0	0		
HBsAg seroconversion	0	0		
Outcomes - HBeAg negative patients	Telbivudine (n=20)	Lamivudine (n=22)		
Serum HBV DNA (mean log 10 reduction from baseline)	-5.5	-4.8	Not reported	Not reported
Patients with undetectable HBV DNA by PCR assay (%)	17 (85)	17/22 (77)	Not reported	Not reported
ALT normalisation (%)	147 (100)	112 (78)	Not reported	Not reported
Viral breakthrough	0	1		
Viral resistance	0	0		
HBsAg loss	0	0		
HBsAg seroconversion	0	0		

Authors' conclusion:

In Chinese patients with chronic hepatitis B, telbivudine treatment for 52 weeks provided greater antiviral and clinical efficacy than lamivudine, with less resistance.

Tenofovir vs. adefovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparisons	Length of follow-up	Outcome measures	Source of funding
Marcellin P, Heathcote EJ, Buti M, et al. 2008	RCT. Randomisation method not reported, but permuted groups of 6 used for group balance. 2:1 randomisation ratio (Tenofovir: Adefovir) Allocation concealment implicit in the use of a centralised	641: Study 102 (HBeAg negative): 375 and Study 103 (HBeAg positive): 266	International study, with patients from 15 countries in 106 clinical sites: North America (31 sites), Europe (60 sites), Asia Pacific (15 sites). Ethnicity predominantly White and Asian. Inclusion: male or female; aged 18-69 years; Hx of CHB, HBeAg seropositive or negative – these were recruited in two separate studies but the results are reported together in this article; compensated liver disease; Knodell necroinflammatory score of 3 or more; all HBsAg positive for 6 months or more prior to screening. For HBeAg (-) patients: serum HBV DNA level > 5 log_{10} copies/mL; ALT 1-10 times ULN; had received < 12 weeks of treatment with any nucleoside or nucleotide OR had received lamivudine or emtricitabine for at least 12 weeks.	Tenofovir 300mg/day for 48 weeks 176 HBeAg (+) 250 HBeAg (-) Loss to follow up/reasons: Seronegative: 6 withdrew before 48 weeks. 5 of these withdrew due to adverse events and one lost to FU. Seropositive:	Adefovir 10mg/day for 48 weeks 90 HBeAg (+) 125 HBeAg (-) Loss to follow up/reasons: Seronegative: 4 withdrew before 48 weeks. No reasons given Seropositive: 5 withdrew before 48 weeks. No reasons given.	48 weeks on treatment	% with HBV DNA <400 copies/mL by PCR (lower limit of detection 169 copies/mL) Incidence of resistance % with ALT normalisation (threshold) % with HBeAg loss and/or seroconversion	Gilead Sciences

	method. Also stratified according to geographic region (Europe, North America, Oceania). Double blinded. This article consisted of reports from 2 closely related studies, that differed in the HBeAg +vity or –vity of its patients. The study results will be reported together in this extraction, and will be clearly marked as seropositive and seronegative. Seropositive:		For HBeAg (+) patients: serum HBV DNA level > 6 log10 copies/mL; ALT 2-10 times ULN; had received < 12 weeks of treatment with any nucleoside or nucleotide Exclusion: co-infection with HIV, Hep C or delta; history or signs of hepatic carcinoma; creatinine clearance level of < 70 ml/min; Hb < 8g/dL, neurophils < 1000/mm^3, liver decompensation or failure. Baseline characteristics: Differences reported as well-balanced	10 withdrew before 48 weeks. All of these withdrew due withdrawal of consent or loss to FU. None lost due to adverse events of lack of efficacy.	NB: supplementary material contains more details plus info on those lost after randomisation but prior to Rx.		% with HBsAg loss and/or seroconversion Histologic improvement	

	HBeAg (+) study		HBeAg (-)study	
	Ten	Ade	Ten	Ade
Median age (sd)	34(11)	34(12)	44(10.6)	43(10)
Sex (% men)	68%	71%	77%	78%
Mean serum HBV DNA (sd), log10 copies/ml	8.64(1.076)	8.88 (0.930)	6.86 (1.31)	6.98 (1.27)
Mean serum ALT (sd), IU/mL	142 (102.81)	155 (121.49)	127.5 (101.21)	163.6(146.02)
Prior use of interferon alfa (%)	17%	14%	17%	18%
Prev Rx with lamivudine or emtricitabi	5%	1%	17%	18%

	Stratified by ALT levels (< or ≥4x ULN). Seronegative: stratified by previous treatment with lamivudine or emtricitabine (< or ≥12 weeks)		ne							
			White Asian Black Other	52% 36% 7% 4%	51% 36% 6% 8%	64% 25% 3% 7%	65% 24% 3% 8%			
			Mean Knodell necroinflammatory score	8.3 (2.14)	8.3 (2.27)	7.8 (2.44)	7.9 (2.18)			
			Genotype (%) A B C D E,F,G,H Other	 24 14 25 32 5 2	 20 11 30 35 3 2	 12 9 12 64 3 3	 11 14 10 63 2 0			

Effect size at 48 weeks

	HBeAg (+) study		HBeAg (-) patient study	
	Tenofovir	Adefovir	Tenofovir	Adefovir
% with HBV DNA <400 copies - ITT	134/176	12/90	233/250	79/125
% with HBV DNA <400 copies – observed data	133/160	12/84	233/241	79/117
Incidence of resistance	Adefovir: rtN236T mutation developed in 1 patient, and rtA181T mutation developed in 3 patients Tenofovir:No DNA changes leading to decreased susceptibility were detected. No genotypic substitutions in polymerase-reverse transcriptase associated with decreased sensitivity to tenofocir were detected at week 48.			
% histologic improvement (%)	131/176 (74)	61/90 (68)	181/250 (72)	86/125 (69)

% with ALT normalisation (<34 IU /mL in women and <43 IU/mL in men)	115/169 (68%)	49/90 (54%)	180/236 (76%)	91/118 (77%)
% with HBeAg seroconversion	32/153 (21%)	14/80 (18%)	NA	NA
% with HBsAg loss	5/158 (3.2%)	0/82 (0%)	0/250 (0)	0/125 (0)
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported			
% withdrawn due to adverse events	0/176	No data reported for seropositive alone, but 3/215 overall for Adefovir	5/250	No data reported for seronegative alone.

Authors' conclusion:.Among patients with chronic HBV infection, tenofovir (300mg/day) had superior antiviral efficacy with a similar safety profile as compared with adefovir (10mg daily) through week 48.

Entecavir vs lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lai 2006	RCT (phase III) No details of	N=638	Patients with HBeAg-negative chronic hepatitis B who had not previously been treated with a nucleoside analogue. Setting: Multicentre-146 centres worldwide (including Europe and middle East (68 centres),	0.5 mg of entecavir once a day for a minimum of 52 weeks. (n=325)	100 mg of lamivudine once a day for a minimum of 52 weeks.	At week 48	Log reduction in the HBV DNA level from baseline % patients	Bristol-Myers Squibb

	randomisation and allocation concealment. Double blind.		Asia (25), Australia (11), North America (30), and South America (12). Inclusion: Eligible patients were 16 years of age older and had HBeAg-negative chronic hepatitis B and compensated liver function (a total serum bilirubin level of 2.5 mg per decilitre (42.8 µmol per litre) or less, a prothrombin time not more than three seconds longer than normal or an international normalised ratio not greater than 1.5, a serum albumin level of at least 3.0 g per decilitre, and no history variceal bleeding or hepatic encephalopathy). Eligible patients also had detectable HBsAg for at least 24 weeks before screening, evidence of chronic hepatitis on a liver biopsy specimen obtained within 52 weeks before randomisation, evidence of HBV DNA by any commercial assay at least 2 weeks before screening, undetectable HBeAg, detectable anti-HBe, a serum HBV DNA level of at least 0.7 MEq per millilitre according to the branched chain DNA assay at screening, and serum alanine aminotransferase level 1.3 to 10 times the upper limit of normal at screening. Exclusion: Co infection with hepatitis C, hepatitis D, or HIV; the presence of other forms of liver disease; use of interferon alpha, thymosin alpha, or antiviral agents with activity against hepatitis B within 24 weeks before randomisation; previous lamivudine therapy lasting more than 12 weeks; an alpha fetoprotein level greater than 100ng	n=311 assigned to entecavir (96%) completed 52 weeks of treatment. No patient discontinued for treatment failure or lack of efficacy by week 52	(n=313) n=296 assigned to receive lamivudine (95%) completed 52 weeks of treatment. No patient discontinued for treatment failure or lack of efficacy by week 52		with undetectable HBV DNA (as measured by Roche COBAS Amplicor polymerase-chain-reaction (PCR) assay (<300 copies per millilitre [lower limit of detection]). Normalisation of serum ALT Primary: Histologic improvement (defined as improvement by at least 2 points in the Knodell necro inflammatory score, with no worsening in the Knodell fibrosis score at week 48, relative to baseline).	

			per millilitre; a history of ascites requiring diuretics or paracentesis; and previous treatment with entecavir. Baseline characteristics				Resistance - viral breakthrough and genotypic mutation (separately) Adverse events	

Characteristic	Entecavir (n=325)	Lamivudine (n=313)
Age (yr)	44±11	44±11
Male sex- no (%)	248 (76)	236 (75)
Knodell necroinflammatory score	8.0±2.7	7.7±2.8
Ishak fibrosis score ≥3 (bridging fibrosis)- % ≥5 (cirrhosis)-%	 43 5	 41 10
Mean HBV DNA level By branched-chain DNA assay-MEq/ml By PCR assay-log copies/ml	 1.2±1.0 7.6±1.8	 1.2±1.0 7.6±1.7
HBeAg-negative-no(%)	322 (99)	309 (99)
Anti-HBe-positive- no (%)	323 (99)	312 (100)
Genotype A	 33 (10)	 33 (11)

B	46 (14)	60 (19)
C	57 (18)	51 (16)
D	157 (48)	135 (43)
Other	32 (10)	34 (11)
ALT IU/L	141 (114.7)	143 (119.4)
Prior anti HBV therapy- no (%)		
Interferon	42 (13)	39 (12)
lamivudine	9 (3)	12 (4)
White	293 (59)	176 (56)
Asian	122 (38)	129 (41)
Black	8 (2)	7 (2)
Other	2 (<1)	1 (<1)

Effect size (Available case analysis)

Outcomes- week 48	Entecavir (n=311)	Lamivudine (n=296)	Difference estimate (95% CI)	p-value
HBV DNA <300copies/ml by PCR assay –no (%)	293/311	225/296		p<0.001
HBV DNA <0.7 MEq/ml by branched chain DNA assay- no (%)	309/311	279/296		p=0.005
Mean change in HBV DNA level from baseline by PCR assay-log copies/ml	-5.0±1.7 n=314	-4.5±1.9 n=295	-0.43 (-0.6 to -0.3)	<0.001
Histological improvement- no (%)*	208/265 (70)	174/250 (61)	96 (2.0 to 17.3)	0.01
Mean knodell necroinflammatory score	4.2	4.6	Not reported	Not reported
Improvement in Ishak fibrosis score -%	36%	38%	Not reported	0.65
ALT normalisation (≤1 x ULN) – no (%)	253/311 (78)	222/296 (71)	6.9 (0.2 to 13.7)	p=0.045
HBsAg loss	1	1		
Viral breakthrough/ rebound* – no (%)	5/325 (2)	25/313 (8)		

YMDD genotypic mutation – no (%)	0/5	20/25 (8)		
Discontinuation due to adverse event, (%) ALT>2xbaseline and >10x ULN, (%) ALT>2 x baseline and >5x ULN	6/325 (2) 3 (<1) 6 (2)	9/313 (3) 5 (2) 10 (3)	Not reported	 0.32 0.50

*From 211 randomly selected patients (ETV + LAM)

Authors' conclusion:

Among patients with HBeAg negative chronic hepatitis B who had not previously been treated with a nucleoside analogue, the rates of histologic improvement, virologic response and normalisation of ALT were significantly higher at 48 weeks with entecavir than with lamivudine. The safety profile of the two agents was similar, and there was no evidence of viral resistance to entecavir.

E.6.1.4 Co-infected with HDV

Peg-IFN-a2a + adefovir vs. adefovir alone vs. Peg-IFN-a2a alone: CHB patients coinfected with HDV

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Wedemeyer 2011 (TO CHECK THE SUPPLEMENTERY	RCT - randomization method unclear	N= 90	Inclusion: Patients 17-80 years old who had HDV infection with compensated liver disease, positive for HbsAg for at least 6 months and positive for anti-HDV antibodies for at least 3 months and positive for HDV RNA on polymerase-chain reaction assay.	Group 1; Peginterferon alfa 2a (180µg weekly) plus adefovir	Group 3; Peginterferon alfa 2a (180µg weekly) (n=29)	48 weeks of treatment + 24 weeks	1) % with clearance of HDV RNA 2)% with ALT normalisation 3) % with	Not reported

APPENDIX)	- blinding unclear -allocation concealment unclear		Exclusion: to check the supplementary Baseline characteristics			(10mg/day) (n=31) Group 2; adefovir (10mg/day) (n=30) Total duration of treatment: 48 weeks Loss to follow up/reasons: 5 in Group 1 and 2 in Group 2	Total duration of treatment: 48 weeks Loss to follow up/reasons: 3 patients	follow up	HBsAg loss and/or seroconversion	

	Peginterferon alfa 2a plus adefovir	Adefovir	Peginterf alfa 2a
Median age (range)	42 (23-59)	33 (21-55)	38 (17-62
HBeAg positive	5 (16%)	4 (13%)	5 (17%)
Sex (% men)	20 (65%)	17(59%)	19 (63%)
Median serum HBV DNA, log10 copies/ml	1.4	2.1	2.6
Median serum ALT, U/L	88	111	73
Cirrhosis	4/29 (14%)	7/29 (24%)	5/25 (20
Previous interferon treatment	12 (38%)	12 (40%)	15(52%)

Effect size

Post-treatment (end of 48 weeks treatment)	Peginterferon alfa 2a (180µg weekly) plus adefovir (10mg/day) (n=26)	adefovir (10mg/day) (n=28)	Peginterferon alfa 2a (180µg weekly) (n=26)	p value
% with clearance of HDV RNA	23%	0	24%	p=0.006 for combination vs. adefovir; p=0.004 for Peginterferon alfa 2a vs. adefovir

% with ALT normalisation	10/26	2/28	8/26	--

Follow up (24 weeks)	Peginterferon alfa 2a (180mg/day) plus adefovir (10mg/day) (n=26)	adefovir (10mg/day) (n=28)	Peginterferon alfa 2a (180mg/day) (n=26)	p value
% with clearance of HDV RNA	28%	0	28%	
% with ALT normalisation	11/26	3/28	13/26	
% with HBsAg loss and/or seroconversion	2/26	Not reported	Not reported	

Authors' conclusion: Treatment with peginterferon alfa 2a for 48 weeks, with or without adefovir, resulted in sustained HDV RNA clearance in about one quarter of patients with HDV infection.

Notes:

IFN-a2b vs. no treatment: CHB patients coinfected with HDV

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rosina 1991	RCT - randomization method: Computer generated randomisation code - blinding	N= 61	Inclusion: adult patients with HBsAg + and antibody to anti-HD in serum and persistently elevated ALT levels (at least 1.5 times the ULN) for at least 1y. All patients had chronic liver disease and positive staining for HDAg on liver biopsy done within 6 months. Exclusion: previous IFN therapy, present or past IV drug use, homosexual preference, pregnancy, serious medical illness other than liver disease (that might preclude completion of the study), hepatic failure with a history of ascites, bleeding esophageal varices,	Recombinant Interferon-a2b subcutaneous injections, three times weekly for 12 months (5 MU/m2 for 4 months	No treatment (n=30) Total duration of treatment: 1 year Loss to	1 year Follow up time post-treatment: 12 months	% with ALT normalisation (biochemical response) % histologic improvement (definition unclear)	Not stated

	unclear -allocation concealment unclear		hepatic encephalopathy, bilirubin, >4mg/dl, serum albumin <3gm/dl, prothrombin time >4sec longer than that of the control, plately count <100,000/mm3, leukocyte count <3000/mm3, granulocyte count <1500/mm3, serum creatinine level >1.7mg/dl, fasting blood sugar >105mg/dl or positive test for antibody to HIV. Baseline characteristics Peginterferon alfa 2b (n=31) / No treatment (n=30) Mean age (SEM): 30 (2) / 29 (2) Male, n: 26 / 28 Mean serum levels (SEM) ALT (IU/L): 164 ±74 / 155 ±91 Bilirubin (µmol/L): 13.7 ±3.4 / 15.4 ±3.4 HDV RNA (no. positive): 15 / 16 HBeAg (no. positive): 6 / 3 HBV DNA (no. positive): 6 / 3 Liver histology Active cirrhosis, n: 10 / 7	and then 3 MU/m2 for a further 8 months (n=31) Loss to follow up/reasons: 5 IFN was discontinued permanently in 5 patients: in one because of an ulcer at the injection site during the 2nd week of therapy, and in another because of acute icteric hepatitis during the 4th month of therapy. 3 treated patients were withdrawn for noncompliance.	follow up/reasons: 8 were withdrawn for noncompliance.			

Effect size

Outcomes assessed at the end of 12 months treatment period	Interferon-a2b (n=26)	No treatment (n=22)
ALT normalisation (%)	8/26 (31)	0/22 (0)
Histologic improvement (%)*	11/19 (57)	5/14 (36)

*The paired specimens coded for chronological sequence were evaluated for change in severity (better, worse, unchanged) of liver disease. Definition of histological improvement unclear.

Authors' conclusion:. Although IFN-alpha in the dosage given in this study had no AV effect on patients with CHD, it reduced hepatic inflammation as measured by ALT levels. Whether a longer duration or reinstitution of IFN-alpha therapy would achieve long-term control of ALT levels and prevent chronic liver damage is not known.

Notes: Mean ALT levels were reported at 24 months.

Interferon alpha 2a vs. no treatment: CHB patients coinfected with HDV

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Farci 1994; Treatment of chronic Hepatitis D with interferon alfa-2a □ 12 years	RCT - randomization method: computer generated - blinding	N= 42	Inclusion: Patients 18-60 years old with a presence of HbsAg, serum antibody to hepatitis delta antigen of the IgG and IgM and serum HDV RNA documented on three occasions within six months before enrollement, histologic evidence of chronic hepatitis and a positive test for intrahepatic hepatitis delta antigen. Exclusion: previous antiviral or immunosuppressive	Group 1; Recombinat interferon alfa 2a (9 million units intramuscularly 3 times/week)	Group 3; No treatment (n=14) 10/13 were followed up to 12 years (3 were treated).	Up to 4 years 41 of the 42 patients (98%) were	1) % with detectable HDV RNA 2)% with ALT normalisation 3) % with detectable HBV DNA (>400	Not reported

follow up study of the same patients by Farci 2004	unclear -allocation concealment: unclear (sealed envelopes)		therapy within 6 months before enrollment, pregnancy or lactation, advanced or decompensated cirrhosis, hepatocellular carcinoma, durg abuse, HIV-1, and other serious medical illnesses. Baseline characteristics INF alfa-2a (9 million units) (N=14) / INF alfa-2a (3million units) (N=14) / No trea (N=14) Mean age in years (SD): 35 (9) / 35 (8) / 37 (12) HBeAg positive (%): 0 / 0 / 2 (14%) HBV DNA (%): 0 / 0 / 1 (7%) Sex (% men): 10 (71%) / 12(86%) / 13(93% Duration of HbsAg seropositivity (months): 59 (45) / 66 (50) / 48 (34) Duration of HDV infection (months): 17 (6) / 20 (10) / 20 (13) Mean serum ALT, U/L (SD): 192 (113) / 209 (136) / 145 (71 Active cirrhosis: 8 (57%) / 7 (50%) / 8 (57%)	(n=14). All 14 patients were followed up to 12 years. Group 2; Recombinat interferon alfa 2a(3 million units intramuscularly 3 times/week) (9 million units) (n=14) 12/14 patients were followed up to 12 years (1 was retreated, 1 was lost to follow up). Total duration of treatment for both groups: 48 weeks	Total duration of treatment: 48 weeks	followed for 6 months, 39 (93%) were followed for a mean of 32 months (range 24-48). 36 (88%) of them were followed up for 12 years.	copies)	

Effect size

Outcomes assessed at the end of 48 weeks treatment	INF alfa-2a (9 million units) (N=14)	INF alfa-2a (3million units) (N=14)	No treatment (N=13)	p value

% with ALT normalisation	10/14 (71%)	4/14 (29%)	1/13 (8%)	-p=0.001 for the comparison with the untreated group/ p=0.029 for the comparison with the low dose group
% with detectable HDV RNA	4/14 (71%)	9/14 (29%)	13/13 (100%)	-p=0.001 for the comparison with the untreated group/
% with detectable HBV DNA (>400 copies)	0/14	1/14	2/13	

6 months follow up	INF alfa-2a (9 million units) (N=14)	INF alfa-2a (3million units) (N=14)	No treatment (N=13)	p value
% with ALT normalisation	7/14 (50%)	1/14 (7%)	1/14 (8%)	-p=0.022 for the comp with the untreated gr p=0.017 for the comp with the low dose gro
% with detectable HDV RNA	8/14 (57%)	12/14 (186%)	12/13 (92%)	-p=0.048 for the comp with the untreated gr
% with detectable HBV DNA (>400 copies)	2/14	2/14	2/13	

Long term follow up (mean 32 months)	INF alfa-2a (9 million units) (N=14)	INF alfa-2a (3million units) (N=13)	No treatment (N=12)	p value
% with ALT normalisation	5/14	0/13	0/12	
% with detectable HDV RNA	0/13	0/13	0/12	

12 years follow up (reported in Farci 2004)	INF alfa-2a (9 million units)	INF alfa-2a (3million units)	No treatment	p value
Survival rate %	86%	39%	31%	
% of patients required liver transplantation	1/14	2/14	5/13	
% with ALT normalisation (among survivers)	7/12	2/4	0/3	
% with detectable HDV RNA (among	12/12	4/4	3/3	

survivers)				
% with detectable HBV DNA (>400 copies) (among survivers)	1/12	1/4	0/3	

Authors' conclusion: The long term follow up confirmed that the efficacy of interferon in chronic Hepatitis D is related to the dose of the drug.

Notes: Serum HDV RNA was determined by a dot blot-hybridization technique with a P labeled Cdna PROBE and the detection limit was < 0.1 pg of cloned DNA.

Interferon alpha 2b vs. Interferon alpha 2b plus lamivudine: CHB patients coinfected with HDV

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Canbakan 2006; Efficacy of interferon a-2b and lamivudine combination treatment in comparison to interferon a-2b alone in chronic delta hepatitis; a randomized trial	RCT - randomization method unclear - blinding unclear -allocation concealment unclear	N= 26	Inclusion: Patients 18-65 years old who had HDV infection (presence of HbsAg , anti-HDV antibodies, HDV RNA on polymerase-chain reaction assay with elevated serum ALT and liver biopsy findings of chronic hepatitis) . Exclusion: presence of decompensated liver disease or hepatocellular carcinoma, pregnancy or lactation, seropositivity for antibody to Hepatitis C or HIV, and presence of other serious illnesses. Baseline characteristics	Group 1; Interferon alfa -2b (10 million units t.i.w) (n=12) Total duration of treatment: 48 weeks	Group 2; Interferon alfa -2b (10 million units t.i.w) plus lamivudine (100 mg/daily) (n=14) Total duration of treatment: 48 weeks	The minimum 96 weeks (rane 2-7.5 years)	1) % with detectable HDV RNA 2)% with ALT normalisation 3) mortality 4) % of patients underwent transplantation	Not reported

	Interferon alfa-2b	interferon alfa 2b+ lamivudin
Mean age (SD) in years	43.83 (8.57)	42.5 (11.2)
Antibody to HBeAg	10 (83.3%)	12 (85.7%)
Sex (% men)	8/12	7/14

			Duration of HbsAg seropositivity (years), mean (SD)	8.16 (5.09)	6.57 (3.39)					
			Duration of HDV infection (years), mean (SD)	5.45 (2.91)	5.42 (2.90)					
			HBV DNA positivity by PCR	1 (8.3%)	1 (7.14%)					
			Cirrhosis	4 (33.3%)	2 (14.3%)					

Effect size

Post-treatment (end of 48 weeks treatment)	Interferon alfa-2b (n=12)	interferon alfa-2b+ lamivudine (n=14)	p value
% with detectable HDV RNA	7/12 (58.2%)	5/14 (35.7%)	--
% with ALT normalisation	5/12 (41.7%)	8/14 (57.1%)	--

Follow up (96 weeks)	Interferon alfa-2b (n=12)	interferon alfa-2b+ lamivudine (n=14)	p value
% with ALT normalisation	2/12	6/14	-
mortality	4/12	1/14	-
Liver transplantation	1/12	1/14	-

Authors' conclusion:. Interferon and lamivudine in combination is encouraging treatment method and may be superior to IFN alone in chronic delta hepatitis.

Notes: Kaplan Meier survival analysis showed a mean survival of 7.38 (1.13) years in the interferon treated group and a mean of 11.38 (1.05) in the combination (interferon + lamivudine) treatment group.

Lamivudine followed by Lamivudine plus Interferon alpha-2a vs. Interferon alpha-2b plus lamivudine: CHB patients coinfected with HDV

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yurdaydn 2008; Treatment of chronic delta hepatitis with lamivudine vs lamivudine + interferon vs interferon	RCT - randomization method unclear - unblinding -allocation concealment reported	N= 26	Inclusion: Patients who had documented hepatitis B and HDV infection of at least 6 months duration respectively. All patients had to have HDV RNA on polymerase-chain reaction assay at the time of screening.. Exclusion: patients with antibody against to hepatitis C or HIV, and presence of other serious illnesses. Baseline characteristics	Group 1; Lamivudine (100 mg daily) for 2 months and then combined with Interferon alfa -2a (9million units t.i.w) (n=14) for 10 months Total duration of treatment: 12 months	Group 2; Interferon alfa -2b (10 million units t.i.w) plus lamivudine (100 mg/daily) (n=14) Total duration of treatment: 48 weeks Loss to follow up/reasons: 3 patients	6 months	1) % with detectable HDV DNA 2)% with ALT normalisation 3) mortality 4) % of patients with histological improvement	Not reported

	Lamivudine + Interferon alfa-2a (N=14)	Lamivudine (N=17)
Median age (range) in years	35 (20-48)	38 (20-55)
HBeAg positive	1/14	1/17
Sex (% men)	10/14	15/17
ALT levels in mean (SD)	113 (49)	92 (66)
HBV DNA levels (copies/ml)	300	600
HDV DNA levels (copies/ml)	5.7 x 106	2.5 x 106
Cirrhosis	4 (in total	

Effect size

Post-treatment (end of 12 months treatment)	Lamivudine + Interferon alfa-2a (N=14)	Lamivudine (N=17)	p value
% with detectable HDV RNA	7/14 (50%)	15/17 (12%)	--
% with ALT normalisation	9/14 (64%)	3/17 (18%)	--
Median reduction in HBV DNA levels (400 copies/ml)	400	400	

Follow up (6 months)	Lamivudine + Interferon alfa-2a (N=14)	Lamivudine (N=17)	p value
% with detectable HDV RNA	9/14 (64%)	15/17 (88%)	-
% with ALT normalisation	3/14 (21%)	4/17 (24%)	-

Authors' conclusion:. Addition of lamivudine to interferon for the treatment of delta hepatitis is of no additional value and that both treatment modalities are superior to lamivudine monotherapy

Notes: The third group of interferon was excluded as n<10.

Lamivudine versus placebo: CHB patients coinfected with HDV

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Niro 2005	RCT Multicentre,	N=31 (29 compl	Hepatitis B surface antigen-positive, HDV RNA positive patients with ALT ≥1.5 times ULN and compensated liver disease	Lamivudine 100mg daily for 52 weeks	Placebo for 52 weeks n=11	52 weeks on randomis	Primary: eradication of serum HDV	Glaxo Smithkline

	Italy and Germany Double blind; pathologist blinded tostudy treatment assessed biopsies Computer-generated randomisation	eted randomised phase of trial but not stated which groups; no paitents withdrew due to adverse events)	Inclusion: Presence of anti-HDV and hepatitis B surface antigen for at least 3 months; detectable HDV RNA at enrolment; ALT ≥1.5 and ≤10 times ULN Exclusion: HCV or HIV positive; had received anti-viral, cytotoxic, corticosteroid or immunomodulatory treatment within 6 months. Baseline characteristics: Lamivudine n=20 / Placebo n=11 Mean (SD) age years: 43.1 (9.5) / 41.7 (8.6) ale n (%): 15 (75) / 9 (82) Mean (SD) ALT (x ULN): 3.2 (1.9) / 3.5 (2.9) Mean ALT U/L: 131 (78) / 143 (118) HDV RNA positive n (%): 18 (90) / 11 (100) HBV DNA > 1000 copies/mL n (%): 7 (35) / 5 (45) Median (IQR) grading score: 6.0 (4.75) / 7.0 (5.0) Median (IQR) fibrosis score: 3.0 (1.5) / 5.0 (4.0)	n=20		ed treatment (then all patients received lamivudine for 52 weeks then 16 weeks off therapy)t	RNA (measured by PCR with sensitivity of 1000 genomes for single PCR and 1-10 genomes for nested PCR) HBsAg loss and seroconversion Secondary: normalisation of ALT Histological response (reduction of ≥2 points on modified Ishak index) Necroinflammatory activity and fibrosis HBV DNA measured by PCR (sensitivity	

							1000 copies/mL) (Resistance in virameic patients at week 104)	

Effect size

Results at week 52 (end of randomised phase)	Lamivudine n=20	Placebo n=11	
HDV RNA positive HDV RNA clearance	20/20 0/20	11/11 0/11	
Mean ALT U/L	86 (41)	98 (53)	

Authors' conclusion: A sustained complete response was achieved in 8% of hepatitis D virus-infected patients treated with lamivudine and a partial histological response in 26% of them. Hepatitis D viraemia was unaffected, even in patients when hepatitis B virus replication was lowered by lamivudine therapy.

Notes: Further results reported after open label lamivudine for all patients (weeks 52-104) and 16 weeks after cessation of treatment (week 120) but not relevant here.

Tenofovir versus adefovir in CHB patients coinfected with HIV

Reference	Study type	Numb	Patient characteristics	Intervention	Comparison	Length of	Outcome	Source

		er of patients				**follow-up**	**measures**	**of funding**
Peters 2006	RCT Multi-site USA Double-blind Study closed early on the basis of pre-specified interim review (when 50% of subjects had reached week 12) as the primary non-inferiority endpoint (tolerance of -1 log $_{10}$ copies/mL) had been reached without safety issues Randomisation:	N=52 At time of SMC review, 35 (67%) had complete week 48; 6 stopped prior to week 48 (none for drug-related toxicity); follow up of 10 truncated for early	Patients with HBV and HIV coinfection on stable ART; serum HBV DNA ≥100,000 copies/mL and plasma HIV-1 RNA ≤10,000 copies/mL; treatment naive or 3TC resistant Inclusion: age 18-65 years; coninfected HBV and HIV-1; stable antiretroviral regimen with HIV-1 RNA ≤10,000 copies/mL for at least 12 consecutive weeks; HBsAg positive; HBV DNA ≥100,000 copies/mL within 12 weeks of study entry; ALT ≤10 x ULN; serum creatinine <1.5mg/dL; serum phosphorus ≥2.2mg/dL; estimated creatinine clearance ≥50mL/min; use of contraception; serum alpha-fetoprotein ≤50ng/dL Exclusion: history of clinically significant renal dysfunction in last 12 months; other liver disease including HCV or HDV; any active medical or psychiatric illness or alcohol or drug usel pregnancy or breast-feeding; malignancy; recipt of systemic corticosteroids, nephrotoxic drugs or anti-HBV drugs except for 3TC within 90- days of study entry. Baseline characteristics: **Tenofovir n=27** / **Adefovir n=25** Median age years: 40 / 47 (p=0.011) Male n (%): 24 (89) / 24 (96)	Tenofovir 300mg daily n=27 Subjects with on-study decline in CPT by 2 points or more were eligible to cross over to alternate regimen in a blinded fashion but none actually crossed over	Adefovir 10mg n=25 Subjects with on-study decline in CPT by 2 points or more were eligible to cross over to alternate regimen in a blinded fashion but none actually crossed over	Median 72 weeks for tenofovir and 78 weeks for adefovir	Primary: initially: change in HBV DNA baseline to week 48; protocol amendment to use time-weighted average instead (DAVG: difference between time-weighted average post-baseline log serum HBV DNA and baseline log serum HBV DNA, using normalised area under curve of log$_{10}$ HBV DNA) Secondary: CPT score; safety/ tolerability; HBeAg	National Institute of Allergy and Infectious Diseases; NIH/NIAID; Adult ACTG Central Group; Birmingham VA Medical Center; NIDDK UCSF Liver Center

	computer generated stratified by Child-Pugh-Turcotte (CPT) score <7 or decompensated liver disease with CPT ≥7) and by CD4 count (<200 or ≥200 cells/mm^3) 58 subjects randomised equally between 2 arms provided 80% power to detect non-inferiority	closure (provided truncated or no DAVG data)	Caucasian n % African American n % HBV DNA log $_{10}$ copies/mL HBeAg positive n % 3TC experienced n % Median ALT IU/mL	15 (56) 9 (33) 9.45 (1.1) 23 (85) 25 (93) 45	14 (56) 8 (32) 8.85 (1.88) 20 (80) 24 (96) 63				seroconversion; ALT	

Effect size

	Tenofovir	Adefovir
HBeAg seroconversion (of those positive at baseline with data at week 48)	1/12	0/15

Authors' conclusion: Over 48 weeks, treatment with either adefovir or tenofovir resulted in clinically important suppression of serum HBV DNA. Both drugs are safe and efficacious for patients coinfected with HBV and HIV.

Notes: Other outcomes provided but unclear denominators in each group

E.6.1.5 Combinations therapies for HBeAg positive treatment-naïve adults with CHB

Adefovir + lamivudine versus lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sung 2008	RCT Randomisation and allocation concealment: unclear Blinding: double blind followed by open label	N=111	HBeAg positive CHB patients, nucleos(t)ide analogue naïve (largely Asians) Inclusion: Aged 18 and over at screening, had detectable HBsAg (at least 6 months prior to study entry), presence of HBeAg, serum HBV DNA $\geq 10^6$ copies/mL using Roche PCR assay, elevated ALT >1.2 x ULN and at least 1 elevated ALT in previous 6 months, adequate renal function (creatinine ≤1.5mg/dL, phosphate >2.4 mg/dL, creatinine clearance ≥60mL/min). Setting: 22 centres (Austria, Canada, France, Germany, Hong Kong, Singapore, Spain, UK and the	Lamivudine (100mg/day) + adefovir (10mg/day) (n=54) Number completed treatment through week 52 and 104: 43 and 40 respectively.	Lamivudine (100mg/day) + placebo (n=57) Number completed treatment through week 52 and 104: 45 and 39 respectively.	52 weeks randomised treatment and 104 weeks (open label) and further 6 months off treatment	Primary: time-weighted average change in HBV DNA from baseline to week 16 (DAVG) Serum HBV DNA $<10^4$ copies/mL and <200	GlaxoSmithKline and Gilead Sciences

	Power calculation provided 100 patients provided 90% power to detect a difference of 0.5 $\log_{10}$ copies/mL (SD 0.71) ITT analysis		US) Exclusion: HBeAg negative, anti-HBs positive, coinfected with HCV or HDV or HIV, had decompensated liver disease, had inadequate haematological function, evidence of pancreatitis, previous use of lamivudine or ADV or any other AV therapy demonstrating anti-HBV activity other than IFN-alpha which could not have been administered within the previous 12 months, could not have received nephrotoxic drug within 2 months prior to study, any investigational drug within 30 days of screening, were not permitted to receive systemic AV agents, cytotoxic agents, immunomodulators or immunosuppressive agents. Baseline characteristics Characteristic | LAM + ADV (n=54) | LAM + placebo (n=57) Age yr-median (range) | 33 (18-63) | 36 (18-79) Male sex (%) | 45 (83) | 42 (74) HBeAg positive, n (%) | 53 (98) | 55 (96) Median HBV DNA (log 10 copies/ml) | 8.87 (6.5-11) | 9.17 (4.4-11.1)	Study duration: 104 weeks (double blind for 1st 52 weeks and patients could receive open label combination therapy from week 52-104 if disease progression occurred or stop treatment at week 52 if HBeAg seroconversion) Lost to follow-up through week 104: 14 Reasons: consent withdrawn (n=1), protocol violation (n=1), lost to follow up (n=2), lack of	Study duration: 104 weeks (double blind for 1st 52 weeks and patients could receive open label combination therapy from week 52-104 if disease progression occurred or stop treatment at week 52 if HBeAg seroconversion) Loss to follow up through week 104: 18 Reasons: consent withdrawn (n=6), adverse event (n=1), lost to follow		copies/mL HBeAg seroconversion HBeAg loss Normalisation of ALT Incidence of resistance (genotypic mutation)	

			ALT, n (%) <2 x ULN 2-5 x ULN >5 x ULN White patients Asian patients, n (%)	 15/53 (28) 26/53 (49) 12/53 (23) 17 (31) 36 (67)	 19/56 (34) 20/56 (49) 17/56 (23) 21 (37) 35 (61)	efficacy (n=1), did not consent to yr 2 (n=8), subject decision (n=1)	up (n=1), lack of efficacy (n=1), disease progression (n=1), did not consent to yr 2 (n=6), subject decision (n=1), randomisation in error (n=1)			

Effect size

Outcomes	LAM +ADV (N=54)	LAM (N=57)
Median change in serum HBV DNA level (range), log 10 copies/ml Week 52 Week 104	 -5.41 (-7.7 to-0.5) (N=47) -5.22 (-7 to 1.6) (N=36)	 -4.80 (-0.8 to -0.1) (N=50) -3.41 (-7.1 to 1.5) (N=36)
Serum HBV DNA<10^4copies/ml) Week 52 Week 104	 31/53 23/53	 29/56 24/56
Undetectable serum HBV DNA <200copies/ml Week 52 Week 104	 21/53 14/53	 23/56 8/56
ALT normalisation, n (%) Week 52 Week 104	 24/51 (47) 23/51 (45)	 39/56 (70) 19/56 (34)

HBeAg loss (%) Week 52 Week 104	 6/52 (12) 10/52 (19)	 12/54 (22) 13/54 (24)
HBeAg seroconversion (%) Week 52 Week 104	 5/52 (10) 7/52 (13)	 9/54 (17) 11/54 (20)
HBV DNA breakthrough	10/53 (19)	24/55 (44)
Incidence of resistance (of those with HBV DNA breakthrough) Genotypic mutation (M204V/I)	4/10	14/24
Incidence of resistance in total Genotypic mutation (M204V/I) Week 52 Week 104	 5/58 (9) 6/41 (15)	 10/51 (20) 15 /35 (43)
Withdrawn study drug due to adverse events, n (%)	0/54	1 /57 (experienced durable HBeAg seroconversion and entered the non-treatment observational arm but was subsequently withdrawn due to elevated HBV DNA levels)

Authors' conclusion: the results of this study demonstrate that two years of lamivudine and adefovir thereapy in NA treatment naïve HBeAg positive CHB patients was associated with a more durable response. The combination group had lower rates of the M204V/I mutation, lower serum HBV DNA levels and higher rates of ALT normalisation compared to the lamivudine monotherapy group. However, these differences were not associated with improvements in HBeAg seroconversion rates.

Notes: only 52 week data relevant to randomised comparison

Interferon alpha 2b + lamivudine versus lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Barbaro et al, 2001	RCT – multicentre open-label Randomisation method: computer generated sequential list of block-randomised assignments maintained by the coordinating centre of the study Blinding: not stated but not blinded (no placebo for IFN injection) Allocation concealment:	N=151	HBeAg positive patients (some were non-responders to a previous treatment with IFN-α2b: 11/76 [16%] in intervention group and 9/75 [12%] controls) Inclusion: patients with detectable HBsAg and HBeAg in serum at the time of screening and for at least the previous 6 months, with serum HBV DNA of at least 5pg/ml and with ALT levels that 1.3-10 x ULN for at least the previous 3 months. Setting: Italy Exclusion: <18 years old; coinfected with HCV or HDV or HIV; decompensated liver disease (bilirubin >2.5 x ULN, prothrmobin time prolonged >3s, albumin <3g/dL, history of ascites, variceal haemorrhage or hepatic encephalopathy); if they had evidence of autoimmune hepatitis (antinuclear antibody titre >1:160) or metabolic liver disease (Wilson's disease, haemochromatosis, deficit of α-1 antitrypsin); if they had received an investigational drug within 30 days before enrolment or any systemic antiviral therapy; immunomodulators, cytotoxic agents or corticosteroids within 6 months before study entry; pregnancy; total WBC <2500/m^3,	IFN α2b (9 MU, three times weekly) plus lamivudine (100mg/day) (n=76) Total duration of treatment: 24 weeks Loss to follow up/reasons: 3 (side effects) (n completed treatment = 73) 3 more lost to follow up (n completed FU = 70)	Lamivudine (100mg/day) (n=75) Total duration of treatment: 52 weeks Loss to follow up/reasons: 4 (side effects) (n completed treatment = 71) 2 more lost to follow up (n completed FU = 69)	48 weeks after treatment period	Primary: loss of HBeAg and undetectable HBV DNA (<1.6 pg/ml) and HBeAg seroconversion (appearance of antibody to HBeAg) at end of treatment; loss of HBsAg and HBsAg seroconversion; sustained suppression of HBeAg and HBV DNA (undetectable through 1-year follow up); sustained normalisation of ALT (≤40UI/L). Secondary: Histologic	Not stated (author stated they had no relationship past or present with the pharmaceutical company involved with the drug mentioned in the study, neither have they received funding

clear

Power calculation provided (75 patients required per group)

ITT analysis

neutrophil granulocyte count <1000/mm^3 and haemoglobin <10g/dl; if they were in poor clinical condition and/or had serious medical diseases.

Baseline characteristics

	IFN-a2b + lamivudine (n=76)	Lamivudine (n=75)
Median age (range)	42 (33-50)	40 (32-47)
Male, n (%)	64 (84)	61 (81)
Median ALT (IU/L) (range)	170 (76-415)	165 (65-398)
Median HBV DNA, pg/ml (range)	166 (10-876)	161 (15-653)
Previous IFN-alpha therapy and non-responders, n (%)	11 (16)	9 (12)
HAI Inflammation score Fibrosis score Cirrhosis, n (%)	11 (5-13) 7 (3-9) 2 (1-3) 4 (5)	11 (7-12) 7 (4-10) 2 (0-3) 3 (4)

improvement (reduction of ≥2 points in the score compared to baseline); safety

Incidence of resistance (YMDD mutation) (viral breakthrough)

from the companies.)

Effect size

	IFN-a2b + lamivudine (n=76)	Lamivudine (n=75)	Comparison

Undetectable HBV DNA at 24 weeks (both groups on treatment), n (%)*	53/76 (70%)	42/75 (56%)	not stated
Undetectable HBV DNA at week 52 (end of monotherapy treatment; follow up for combination group), n (%) (ITT)*	28/76 (37%)	23/75 (31%)	not stated
HBeAg seroconversion and undetectable HBV DNA at end of treatment period (24 or 52 weeks, respectively)	27/76 (35)	14/75 (19)	p=0.042
Viral breakthrough, n (%) during treatment	3/76 (4%)	2/75 (3%)	
HBeAg seroconversion and undetectable HBV DNA at end of follow up (76 week and 100 weeks, respectively), n (%)	25/76 (33)	11/75 (15)	p=0.017
HBsAg loss, n (%)	0 (0)	0 (0)	not stated
ALT normalisation during treatment and sustained through follow up, n (%)	28/76 (37)	17/75 (23)	not stated
Histologic improvement, n (%) (ITT)**			
Inflammation score	35/76 (46)	20/75 (27)	p=0.021
Fibrosis score	32/76 (42)	18/75 (24)	p=0.002
Incidence of resistance (YMDD mutation)***	9/70 (13)	11/68 (16)	p=0.796
Discontinued IFN due to adverse events****, n	3	4	

*values for undetectable HBV DNA were approximated from graph.

**patients who had missing biopsy data were counted as no response.

***6/9 in combined group and 8/11 in LAM group were non-responders to previous IFN treatment with IFN a2b. YMDD mutations were not associated with a decreased histologic response.

****Side effects within an average of 10 weeks (4-16 weeks) from enrolment

Notes: different treatment durations (combined therapy = 24 weeks; LAM therapy = 52 weeks).

Authors' conclusion: Six-month treatment with IFNα2b and lamivudine in combination appeared to increase the rate of sustained HBeAg seroconversion compared to 1 year lamivudine monotherapy. However the potential benefit of combining LAM and IFN should be investigated further in studies with different regimens of

combination therapy.

IFN alpha 2a/2b + lamivudine vs lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jang et al, 2004	RCT – long term therapy Randomisationmethod: unclear Blinding: unclear Allocation concealment: unclear No sample size calculation provided	N=83	HBeAg positive patients who were not responsive to IFN-a2b therapy (5MU subcutaneous injection three times weekly for at leat 4 months) Inclusion: biopsy proven CHB; positive for HBsAg, HBeAg and HBV DNA for at least 6 months before the therapy; had no previous history of lamivudine use; ALT ≥2 x ULN Setting: Korea Exclusion: HCV/HDV/HIV; patients who showed liver cirrhosis by histological or clinical examination Baseline characteristics IFN alpha+ lamivudine (n=41) / Lamivudine (n=42) Mean age ±SD (years): 35 ±8 / 39 ±9 Male, n (%): 36 (88) / 32 (76)	Lamivudine in combination with IFN alpha (5MU, three times weekly) until HBV DNA were persistently undetectable for 6 months or until viral breakthrough occurred (n=41) Total duration of treatment: IFN used until serum HBV DNA was persistently undetectable for 6 months or until viral	Lamivudine monotherapy (100mg/day) until HBeAg/ HBV DNA negativity achieved. (n=42) Total duration of treatment: median 38 (range 12-60) months LAM stopped in patients whose serum HBV DNA and	6, 12, 36 and 48 months after starting lamivudine therapy	Primary: undetectable HBV DNA using solution hybridisation assay (lower limit of detection 1 pg/ml) Secondary: % with ALT normalisation; HBeAg loss Incidence of resistance -YMDD mutation - viral breakthrough, defined as reappearance	Not stated

			Mean ALT ± SD (IU/L)	242 ±175	263 ± 183	breakthrough occurred (median 7, range 7-13 months); LAM stopped in patients whose serum HBV DNA and HBeAg had been negative for 24 months persistently. (median 26, range 5-60 months) Loss to follow up/reasons: 2 lost to follow up + 3 stopped due to side effects + 1 stopped due to desire to conceive	HBeAg had been negative for 24 months persistently. Loss to follow up/reasons: 2 lost to follow up		of HBV DNA in at least 2 consecutive tests during LAM therapy following the disappearance of HBV DNA	
			Log HBV DNA (pg/mL)±SD	2.4±0.7	2.3±0.7					
			YMDD mutant	0/29	0/38					
			Histological activity n (%): Mild Moderate Severe	 12 (29) 22 (54) 7 (17)	 13 (31) 21 (50) 8 (19)					
			Median (range) prior duration of IFN	11 (4-18)	6 (4-12)					

Effect size

6 months after starting lamivudine treatment	IFN alpha + lamivudine (n=41)	Lamivudine (n=42)
Undetectable HBV DNA	40/41 (97%)	42/42 (100%)
% with ALT normalisation	37/41 (90%)	41/42 (97%)
HBeAg loss	9/41 (22%)	9/42 (21%)
Viral breakthrough	2/41 (5%)	2/42 (5%)
Discontinued study drugs (IFN) due to adverse events	3 (several myalgia, n=2; depression, n=1)	0

12 months after starting lamivudine treatment	IFN alpha + lamivudine (n=41)	Lamivudine(n=42)

Undetectable HBV DNA by PCR	41/41 (100%)	42/42 (100%)
% with ALT normalisation	41/41 (100%)	42/42 (100%)
HBeAg loss	19/41 (46%)	12/42 (29%)
Viral breakthrough	2/41 (5%)	4/42 (10%)

24 months after starting lamivudine treatment	IFN alpha + lamivudine (n=41)	Lamivudine (n=42)
Undetectable HBV DNA by PCR	41/41 (100%)	42/42 (100%)
% with ALT normalisation	41/41 (100%)	42/42 (100%)
HBeAg loss	25/41 (61%)	17/42 (41%)
Viral breakthrough	8/41 (20%)	23/42 (55%)

36 months after starting lamivudine treatment	IFN alpha + lamivudine (n=41)	Lamivudine (n=42)
HBeAg loss	28/41(67%)	18/42 (44%)
Viral breakthrough(of the 74 completely followed up)	9 (30%)	22 (58%)
Incidence of resistance - YMDD mutation	5/9 (56%)	18/22 (82%)

Authors' conclusion: IFN-alpha combined with lamivudine may reduce viral breakthrough during long-term lamivudine therapy, probably by suppressing the appearance of YMDD mutants.

Interferon alpha 2a/2b + lamivudine vs interferon alpha 2a/2b

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Cindoruk et al, 2002	RCT – phase III Randomisatio	N= 100 (61 men and 30 women)	HBeAg positive (treatment naïve) patients Inclusion: patients with elevated ALT for ≥6months, were HBV DNA positive, HBeAg	IFN-alpha 9 million units 3 times weekly in combination with	IFN-alpha 9 million units 3 times	6 months treatment + 6	% with undetectable HBV DNA,	Not stated

	n method: unclear ratio 1:1 Blinding: Double-blind Allocation concealment: unclear No sample size calculation provided		positive, had a liver biopsy within 6 months of enrolment that indicated histologic evidence of chronic hepatitis. Setting: gastroenterology unit of a hospital, one of the referral centres in Turkey. Exclusion: decompensated cirrhosis, psychiatric conditions, diabetes mellitus, autoimmune diseases, concurrent hepatitis C or D or HIV, high alcohol intake, concurrent IV drug abuse,previous treatment with IFN, pregnancy, or concomitant significant medical illness. Baseline characteristics IFN-alpha + lamivudine (n=50) / IFN-alpha (n=50) Mean age (SE): 34 (13) / 35 (13) Male, n: 32 / 29 Female, n: 18 / 21 Cirrhosis: 0 / 0 ALT level, U/L (range): 121 (69) / 142 (83) Knodell score: 7 (4) / 8 (5) Duration of illness, mean (SD), months: 17 (9) / 21 (14)	100mg/day lamivudine (n=50) Total duration of treatment: 6 months Loss to follow up/reasons: 0	weekly alone (n=50) Total duration of treatment: 6 months Loss to follow up/reasons: 0	months follow up	measured by PCR % with ALT normalisation % with HBeAg seroconversion complete respons: HBV DNA negative and normal ALT at months 6 and 12; partial response: HBV DNA positive at end of treatment and normal ALT and month 6 and 12; no response: HBV DNA positive and elevated ALT at months 6 and 12	
Effect size								

At the end of treatment at 6 months	IFN-alpha + lamivudine (n=50)	IFN-alpa (n=50)	Comparison
% with undetectable HBV DNA	26/50 (52%)	24/50 (48%)	not stated
% with ALT normalisation	43 (86%)	28 (56%)	p<0.05

Follow up at 6 months (12 months in all)	IFN-alpha + lamivudine (n=50)	IFN-alpa (n=50)	Comparison
% with ALT normalisation	32 (64%)	24 (48%)	p<0.05
% with undetectable HBV DNA	25 (50%)	21/50 (42%)	NS
HBeAg seroconversion, n (%)	15 (30%)	11 (22%)	NS
Response: Complete Partial None	 24 (48%) 10 (20%) 16 (32%)	 21 (42%) 10 (20%) 16 (32%)	 p<0.05 p<0.05 p<0.05

Authors' conclusion:. Concurrent combination therapy with IFN alpha and lamivudine has a more beneficial effect on biochemical parameters (i.e. ALT levels) than on viral parameters (i.e. HBV DNA, seroconversion to anti-HBeAg) and this effect is more pronounced after 1 year of treatment than after 6 months. Further studies are needed to determine the long-term effects of combination therapy with lamivudine and IFN alpha.

IFN alpha 2a + lamivudine vs INF alpha 2a

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ayaz et al, 2006	RCT Randomisatio	N= 68	HBeAg positive patients (treatment naïve) Inclusion: Presence of HBsAg in serum for ≥6	IFN-a2a 9 million units 3 times weekly in combination with	IFN-a2a 9 million units 3 times	12 months on treatme	% with undetectable HBV DNA,	Not stated

	n method: unclear Randomised in 1:1 ratio Blinding: unclear Allocation concealment: unclear		months, presence of HBeAg, absence of anti-HBs and anti-HBe, ALT >1.5 x ULN (40IU/L), presence of HBV DNA, and histological evidence of chronic hepatitis on liver biopsy taken within 6 months prior to enrolment. Setting: Turkey Exclusion: prior treatment for CHB with IFN-alpha or another AV or immunosuppressive drug; coinfected with HCV, HDV or HIV; another cause of chronic liver disease; alcohol intake >40g/day, evidence of hepatocellular cancer; decompensated liver disease; any contraindication to the use of IFN-alpha; pregnancy; abnormal haematological tests; lack of informed consent. Baseline characteristics IFN-alpha + lamivudine (n=31) / IFN-alpha (n=33) Mean age (SD) years: 31.6 (8.2) / 28.4 (7.2) Male, n (%): 24 (77) / 21 (63) Mean (SD) ALT level, IU/L (SD): 124 (59) / 128 (57) Mean HBV DNA (pg/dL), range: 3142 (47-4213) / 2912 (65-4412)	100mg/day lamivudine (n=33) Total duration of treatment: 12 months Loss to follow up/reasons: 2 did not complete study due to side effects (depression and hematological toxicity; 3 at week 10 and one at week 12 across the two groups)	weekly alone (n=35) Total duration of treatment: 12 months Loss to follow up/reasons: 2 did not complete study due to side effects (depression and hematological toxicity; 3 at week 10 and one at week 12 across the two groups)	nt plus 6 months post treatment	measured by PCR (lower limit of detection 5pg/mL) ALT normalisation HBeAg seroconversion HBsAg loss Complete response: HBeAg to anti-HBeAg conversion, clearance of HBV DNA and normalisation of ALT	

			Mean HAI (range)	8.2 (6-10)	7.7 (6-10)					

Effect size

Post-treatment at 12 months	IFN-a2a + lamivudine (n=31)	IFN-a2a (n=33)	Comparison
% with undetectable HBV DNA	28/31 (90%)	22/33 (67%)	p=0.047
ALT normalisation, n (%)	20 (65)	17 (52)	NS
HBeAg seroconversion	4 (13)	4 (12)	NS
HBsAg loss/seroconversion, n	0	0	
Discontinued study treatment due to adverse events, n	2	2	

Follow up at 6 months	IFN-a2a + lamivudine (n=31)	IFN-a2a (n=33)	Comparison
% with undetectable HBV DNA	26/31 (84%)	10/33 (30%)	p=0.034
ALT normalisation, n (%)	13 (42)	9 (27)	p<0.05
Complete response	13/31 (42%)	8/33 (24%)	NS

Authors' conclusion: Combination treatment with IFN-alpha and lamivudine was better than IFN-alpha monotherapy in ALT normalisation and HBV DNA clearance; however, it did not have a better sustained response rate than IFN-alpha alone.

IFn alpha 2a + lamivudine vs INF alpha 2b

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yalcin 2003	RCT- unblinded -no details on randomization method - unclear allocation concealment	N= 49	HBeAg positive patients (treatment naïve) Inclusion: Patients aged 18-60 years with a positive serum test result for hepatitis B surface antigen (HbsAg) and HBeAg, with a positive serum test result for HBV DNA by liquid hybridization or PCR, and elevated serum alanine transaminase (ALT) level (>1.5 -10 times greater than the upper limit of the normal on 3 occassions during the 6 months before enrollment, and a liver biopsy specimen obtained from the patient demonstrated histologic evidence of chronic HBV infection. Exclusion: if patients had been treated previously with IFN or had received antriviral or immunosuppressive medications, if they were coinfected with C, delta or HIV, if they had other causes of chronic liver disease, if they drank >40 gr of alcohol per day, if they had evidence of hepatocellular carcinoma, if they had decompensated liver disease, pregnant women, contraindications to IFN, total leucocyte count <2500 cells/mm^3, neutrophil granulocyte count <1000 cells/mm^3, platelet count <100,000 cells/mL, Hb <10g/dL, no consent. Baseline characteristics Interferon alfa-2b plus lamivudine (n=33) | Interferon alfa-2b (n	Interferon alfa-2b (10 million U 3 times/ week) plus lamivudine (100 mg daily) (n=33) Total duration of treatment: 12 months Loss to follow up/reasons: none	Interferon alfa-2b (10 million U 3 times/ week) (n=16) Total duration of treatment: 12 months Loss to follow up/reasons: 1 was lost to follow up	Minimum 12 months (median follow up period for the combination: 26.5 months and for the monotherapy: 27 months)	1) % with undetectable HBV DNA (<10^3-10^4 copies/ml) by PCR 2)% with HBeAg seroconversion 3)% with ALT normalisation 4) Histological improvement (decrease of at least 2 points in the Knodell histological activity index (HAI) necroinflammation score)	Not reported

Median age (range)	23 (16-60)	24 (16-41))
Median weight (range), kg	66 (48-94)	64 (50-91)
Sex (% men)	22/33	12/16
Median serum HBV DNA (range), log10 copies/ml	3258 (22-6674)	2866 (23-5792)
Median serum ALT (range), U/L	140 (50-356)	153 (58-240)
Hepatic inflammation, HAI (median (range))	8 (4-14)	9.5 (4-13)

Effect size

After 6 months of treatment	Interferon alfa-2b plus lamivudine (n=33)	Interferon alfa-2b (n=15)	p value
% with HBeAg seroconversion	18/33	5/15	NS
% with undetectable HBV DNA (<10^3-10^4 copies/ml)	32	6	p=0.001
% with ALT normalisation	18	5	NS

Post-treatment (end of 12 months treatment)	Interferon alfa-2b plus lamivudine (n=33)	Interferon alfa-2b (n=15)	p value
Log reduction of HBV DNA	Not reported	Not reported	--
% with undetectable HBV DNA (<10^3-10^4 copies/ml)	33	9/15	P=0.001
Incidence of resistance	Not reported	Not reported	-
% with ALT normalisation	28/33	11/16	NS

% with HBeAg seroconversion	22/33	7/16	P=0.222
% with HBsAg loss and/or seroconversion	2/31	0/15	--
Histological improvement	26/31	4/15	P<0.001
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	--
% withdrawn due to adverse events	none	none	-

Follow up (12 months follow up)	Interferon alfa-2b plus lamivudine (n=33)	Interferon alfa-2b (n=15)	p value
Log reduction of HBV DNA	Not reported	Not reported	-
% with undetectable HBV DNA (<10^3-10^4 copies/ml)	15/33	3/15	P=0.133
Incidence of resistance	Not reported	Not reported	-
% with ALT normalisation	16/33	3/15	P=0.060
% with HBeAg seroconversion	18/33	3/15	P=0.039
% with HBsAg loss and/or seroconversion	Not reported	Not reported	-
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	-
% withdrawn due to adverse events	none		

Authors' conclusion: Combination therapy increased the rate of sustained suppression of HBeAg and resulted in significant improvement in Knodell histologic activity index scores, compared with monotherapy. However, there was no significant difference in rates of sustained suppression between the 2 groups at the end of follow up.

Peg interferon alpha 2b + lamivudine vs peg IFN alpha 2b

Reference	Study type	Number of	Patient characteristics	Intervention	Comparison	Length of	Outcome measures	Source of

		patients				follow-up		funding
Janssen HLA, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, Simon C, So TMK, Gerken G, de Man R, Niesters HGM, Zondervan P, Hansen B, Schalm SW. Pegylated interferon alfa-2b alone or in combination with lamivudine for	RCT Randomisation done centrally Stratified by study centre, (blocks of 6 per centre). Actual method of randomisation not described. Double blinded. Power calculation: 270 patients required for power of 80% (α=0.05) to detect difference between monotherapy 20% and combination therapy 36% in rate of HBeAg loss at end of follow up	N= 307 randomised	Setting: 42 centres in 15 countries in Europe, East Asia, North America. Inclusion: Aged 16 or older; Positive for HBsAg > 6 months; positive for HBeAg on at least 2 occasions within 8 weeks before randomisation; at least 2 episodes of raised ALT (2x ULN) within the 8 weeks prior to randomisation. Exclusion: Hep C, Hep D or HIV antibodies; antiviral or immunosuppressive therapy in the last 6 months; pregnancy or inadequate contraception; substance abuse within last 2 years; other causes of liver disease; co-existing serious medical or psychiatric illness; uncontrolled thyroid disease; low leucocyte (≤3x10^9/L), granulocyte (≤1.8x10^9/L) or platelet (≤100 x10^9/l) counts; liver ca; advanced liver disease with prothrombin time prolonged > 3 secs, serum albumi <35 g/L, bilirubin >35 micromol/L, or a history of ascites, variceal bleeding, or hepatic encephalopathy. Baseline characteristics: Characteristics described as "similar": **Peg alpha 2b + LAM (n=130) / Peg alpha 2b (n=136)** Mean age (sd): 34(12) / 36(14) Mean weight (sd), kg: 74(16) / 72(13) Sex (% men): 75% / 79% Mean serum	Peg alpha 2b + Lamivudine (LAM); weekly doses of 100microg Peg alfa-2b and a daily dose of 100mg/day LAM. Dose of Peg alfa 2b reduced to 50microg / week at 32 weeks (n=152 randomised, 130 analysed in modified ITT analysis; Of the 22 not analysed, 4 did not start Rx, 6 were HBeAg at start of treatment, 12 withdrawn due to poor	Peg alfa 2b + placebo (similar in appearance to LAM); weekly doses of 100microg Peg alfa-2b and placebo. Dose of Peg alfa 2b reduced to 50microg / week at 32 weeks (n=155 randomised, 136 analysed in modified ITT analysis; Of the 19 not analysed, 3 did not start Rx, 4 were HBeAg at start of treatment, 12 withdrawn due to poor	At 78 weeks (26 weeks post Rx cessation).	Measured at 52 and 78 weeks. 1) % with HBV DNA <200,000 copies/mL or <400 copies/mL (lower limit of detection by PCR) 2) Incidence of resistance 3)% with ALT normalisation 4)% with HBeAg loss (primary) and/or seroconversion 5)% with HBsAg loss and/or seroconversion	Schering-Plough International; GlaxoSmithKline. Each centre run by an independent company.

HBeAg-positive chronic hepatitis B: a randomised trial. The Lancet 2005; 365: 123-129.			HBV DNA (sd), log_{10} copies/ml Mean serum ALT (sd), U/L Previous interferon therapy Previous LAM therapy Ethnicity White Asian Other/mixed Genotype: A B C D Other	 4.4(3.9) 27/130 17/130 95/130 24/130 11/130 43 (33%) 11 (9%) 18 (14%) 52 (40%) 6 (4%)	 4.3(3.1) 28/136 16/136 101/136 29/136 6/136 47 (35%) 12 (9%) 21 (15%) 51 (38%) 5 (4%)	conduct of a centre) Total duration of treatment: 52 weeks Loss to follow up/reasons: 13 discontinued early; 12 due to adverse events, 1 other reasons. Of these 3 lost to FU (thus results were imputed for these 3 – as non-responders) 114 completed treatment + follow up	conduct of a centre) Total duration of treatment: 52 weeks Loss to follow up/reasons: 11 discontinued early; 11 due to adverse events. Of these 7 lost to FU (thus results were imputed for these 7 – as non-responders) 118 completed treatment and follow up			

Effect size: All ITT

Post-treatment	Peg alfa 2b + Lamivudine (n= 130)	Peg alfa 2b (n=136)	p value

Log reduction of HBV DNA	-	-	-
HBV DNA <200,000 copies/mL	96/130	40/136	<0.0001
% with undetectable HBV DNA (<400 copies/mL)	43/130	13/136	<0.0001
Incidence of resistance YMDD mutant	 14/130	 no data given; assume 0	
% with ALT normalisation	66/130	46/136	0.005
% with HBeAg loss	57/130	40/136	0.01
% with HBeAg seroconversion	33/130	30/136	0.52
% with HBsAg loss	9/130	7/136	0.54
% with HBsAg seroconversion	8/130	6/136	0.53
Quality of life measures (EQ-5, SF-35, liver disease specific)	-	-	-
Histology: fibrosis score improved inflammation improved	 17/52 25/52	 13/58 31/58	
% withdrawn due to adverse events	12/130	11/136	

Follow up (week 78)	Peg alfa 2b + Lamivudine (n= 114)	Peg alfa 2b (n=118)	p value
Log reduction of HBV DNA	-	-	-
HBV DNA <200,000 copies/mL	41/114	37/118	0.44
% with undetectable HBV DNA (<400 copies/mL)	12/114	9/118	0.43
Incidence of resistance	NA	NA	
% with ALT normalisation	46/114	44/118	0.60
% with HBeAg loss	46/114	49/118	0.91
% with HBeAg seroconversion	38/114	39118	0.92
% with HBsAg loss	9/114	9/118	0.92

% with HBsAg seroconversion	9/114	7/118	0.54
Quality of life measures (EQ-5, SF-35, liver disease specific)	-	-	-
% withdrawn due to adverse events	NA	NA	

Authors' conclusion: Treatment with pegylated interferon alfa-2b is effective for HBeAg-positive chronic hepatitis B. Combination with lamivudine in the regimen used is not superior to monotherapy.

Peg IFN alpha 2b + Lamivudine vs lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chan et al, 2005	RCT – phase III Randomisation method: computer generated list; ratio 1:1 Blinding: open-label Allocation concealment: research staff who were not involved in	N= 100	HBeAg positive treatment naïve patients (1 patient was HBeAg negative) Inclusion: 18-65y, HBeAg positive, HBsAg positive for at least 6 months, had a serum HBV DNA level of at least 500,000 copies/mL and ALT that was 1.3 to 5 x ULN. Setting: outpatient clinic (single centre) in a secondary referral centre, Hong Kong, China Exclusion: decompensated liver disease or a history of IFN or antiviral agent use. Coinfection with HCV or HDV or HIV; history of hepatocellular carcinoma; other causes of liver disease, including autoimmune hepatitis; Wilson disease; hemochromatosis and α1-antitrypsin deficiency;	Combination: peg-IFN α2b (given as a subcutaneous injection at a dosage of 1.5 µg/kg of body weight/ week for patients who weighed <65kg or 100µg/week for patients who weighed>65kg for 32 weeks) was administered 8 weeks before lamivudine was	Lamivudine 100mg/day (n=50) Total duration of treatment: 52 weeks Did not complete treatment/ reasons: 2 (lack of	end of treatment + 24 weeks follow up	Reduction in HBV DNA % with undetectable HBV DNA (<10^2 copies/ml) by PCR % with ALT normalisation % with HBeAg loss % with HBeAg seroconversion	Schering-Plough Corp. supplied peg-IFN α2b and GSK supplied lamivudine

	patient management placed the random numbers in opaque envelopes. A research nurse prescribed study drugs after receiving the info about treatment allocation at the baseline visit. Sple size calculation provided: 94 patients required to provide 80% power at α=0.05, allowing for dropout rate of 10% to detect a response rate 30% higher in combination group than monotherapy		serious medical or psychiatric illness; concurrent use of corticosteroid or immunosuppressive agents; and pregnancy. Baseline characteristics IFN-alpha a2b + lamivudine (n=50) / lamivudine (n=50) Median age (range): 32 (19-57) / 34 (21-65) Male, n (%): 31 (62) / 36 (72) Median BMI, kg/m2 (range): 22 (16-33) / 25 (18-32) Median ALT level, U/L (range): 144 (48-1179) / 119 (36-461) Normal ALT, n (%): 2 (4) / 3 (6) Median HBV DNA, log_{10} copies/mL (range): 8.04 (5.91-9.74) / 7.67 (5.74-9.49) HBV genotype, n (%) B: 15 (30) / 16 (32) C: 32 (64) / 31 (64) B&C: 3 (6) / 3 (6) Histology Necroinflammation score: 5 (1-11) / 5 (1-12) Fibrosis score, 1 (0-6) / 1(0-5)	administered. Then both treatment were given in combination for 24 weeks, followed by lamivudine monotherapy for a further 28 weeks (n=50) Total duration of treatment: 60 weeks (duration of combination therapy: 24 weeks) Did not complete treatment/ reasons: 2 (lack of interest, n=1; allergic reaction, n=1) Completed post-treatment follow up: 43 Note: open-label lamivudine was	interest, n=1; pregnancy, n=1) Completed post-treatment follow up: 37 No patients in lamivudine group received peg-IFN during study period		% HBsAg loss HBsAg seroconversion Incidence of resistance Histologic improvement (necroinflammatory score and fibrosis score separately) Adverse events	

			median (range)			given to patients who experienced severe post-treatment relapse of CHB.				

Effect size (ITT analysis was conducted)

Post-treatment (combination therapy – 60 weeks; monotherapy therapy – 52 weeks)	Peg-IFN-a2b + lamivudine (n=48)	lamivudine (n=48)	Median difference (95% CI)
Virologic response (HBeAg loss and seroconversion and HBV DNA <500,000 copies/mL)	30 (60%)	14 (28%)	32% (14-50%), p=0.001
Median reduction in HBV DNA, copies/mL (range)	3.89 (1.59 to 6.35)	2.74 (-0.10 to 5.68)	1.24 (0.78 to 1.66)
% with HBV DNA $<10^2$ copies/ml by PCR, n	5/48	2/48	
Incidence of resistance Lamivudine resistant mutant only, n Both wild type and lamivudine resistant mutant, n	10/48 (21%) 5 5	19/48 (40%) 7 12	
% with ALT normalisation	45/50 (90%)	39/50 (78%)	
Histologic improvement Necroinflammatory score Fibrosis score	 4/40 4/40	 4/44 2/44	
% with HBeAg loss	30 (60%)	14 (28%)	
% with HBeAg seroconversion (to anti-HBe) (%)	30 (60%)	14 (28%)	
% with HBsAg loss	1	0	
% withdrawn due to adverse events	1 *	0	

*One patient had received only 7 doses of peg-IFN withdrew from the study and was considered to have treatment failure. Peg-IFN was stopped in an additional 3 patients but lamivudine was continued until week 60. Another 5 patients required reduction of dosage of Peg-IFN due to adverse events; another patient had peg-IFN withheld for 2 doses at weeks 4 and 5 due to severe hepatitis flare up.

Assessed at week 48* (during treatment)	Peg-IFN-a2b + lamivudine (n=48)	lamivudine (n=48)	Median difference (95% CI)
Virologic response (HBeAg loss and seroconversion and HBV DNA <500,000 copies/mL	25/50 (50%)	14/50 (28%)	
Median reduction in HBV DNA, copies/mL (range)	4.65 (-0.84 to 7.83)	3.62 (1.32 to 7.33)	1.10 (0.55 to 1.65)

*Treatment duration in the combination treatment group was 8 weeks longer than the duration of lamivudine monotherapy group. Changes in HBV DNA levels were compared when patients in both groups finished 48 weeks of treatment.

Assessed at 24 weeks follow up (post-treatment)	Peg-IFN-a2b + lamivudine (n=43)	lamivudine (n=37)	Median difference (95% CI)
Virologic response (HBeAg loss and seroconversion and HBV DNA <500,000 copies/mL)	18 (36%)	7 (14%)	
Median reduction in HBV DNA, copies/mL (range)	4.65 (-0.84 to 7.83)	3.62 (1.32 to 7.33)	1.10 (0.55 to 1.65)
% with undetectable HBV DNA (<10^2 copies/ml) by PCR, n	3/43	2/37	
% with ALT normalisation	25/50 (50%)	15/50 (30%)	

Authors' conclusion: In patients with HBeAg positive chronic hepatitis B, staggered combination treatment with peg-IFN-a2b and lamivudine may lead to a higher rate of virologic response than lamivudine monotherapy.

Notes:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chan et al, 2005A	Long term follow up study of a RCT (Chan 2005) Randomisatio	N= 95	HBeAg positive* treatment naïve patients *At the end of treatment, 30 patients in the combination arm became HBeAg (-) and 13 patients in the lamivudine monotherapy arm became HBeAg (-).	Combination: peg-IFN a2b (given as a subcutaneous injection at a dosage of 1.5	Lamivudine 100mg/day (n=47)	Post treatment follow up of at least 52	% with continuing detectable HBV DNA (≥500,000 copies/ml) by	Not stated

	nmethod: computer generated list; ratio 1:1 Blinding: open-label Allocation concealment: research staff who were not involved in patient management placed the random numbers in opaque envelopes. A research nurse prescribed study drugs after receiving the info about treatment allocation at the baseline visit. No sample size calculation provided		Inclusion: 18-65y, HBeAg positive, had a serum HBV DNA level of at least 500000 copies/mL and ALT that was 1.3 to 5 x ULN. Setting: outpatient clinic (single centre) in a secondary referral centre, Hong Kong, China Exclusion: decompensated liver disease or a history of IFN or antiviral agent use. Coinfection with HCV or HDV or HIV; history of hepatocellular carcinoma; other causes of liver disease, including autoimmune hepatitis; Wilson disease; hemochromatosis and α1-antitrypsin deficiency; serious medical or psychiatric illness; concurrent use of corticosteroid or immunosuppressive agents; and pregnancy. Baseline characteristics* IFN-alpha a2b + lamivudine (n=48) / lamivudine (n=47) Mean age (SD): 32 (10) / 35 (10) Male, n (%): 29 (60) / 34 (72) Mean BMI, kg/m2 (SD): 22.7 (4) / 24 (3.8) Mean ALT level, U/L (range): 140 (48-1179) / 118 (36-461) Mean log HBV DNA, copies/mL (SD): 8.2 (1) / 7.9 (1.1)	µg/kg of body weight/ week for patients who weighed <65kg or 100µg/week for patients who weighed>65kg for 32 weeks) was administered 8 weeks before lamivudine was administered. Then both treatment were given in combination for 24 weeks, followed by lamivudine monotherapy for a further 28 weeks (n=48) Total duration of treatment: 60 weeks (duration of combination therapy: 24 weeks) The post treatment follow	Total duration of treatment: 52 weeks The post treatment follow up of patients who received lamivudine monotherapy was 124±29 weeks. Loss to follow up/reasons: unclear No patients in lamivudine group received peg-IFN during study period	weeks	PCR % with ALT normalisation % with HBsAg loss	

			HBV genotype, n (%) B C B&C Histology Necroinflammation score Fibrosis score, median (range) *all patients had baseline liver biopsy	 15 30 3 5 (1-10) 1 (0-6)	 16 28 3 5 (1-12) 1(0-5)	up of patients who received combination treatment was 117±34 weeks. Loss to follow up/reasons: unclear Note: open-label lamivudine was given to patients who experienced severe post-treatment relapse of CHB.				

Effect size (ITT analysis was conducted)

At least 52 weeks post-treatment follow up	Peg-IFN-a2b + lamivudine (n=48)	lamivudine (n=47)
Duration of follow up, weeks	117 (34)	124 (29)
Sustained response*, n	14	4
Viral relapse (HBV DNA >1,000,000 copies/mL)	16	9
% with continuing detectable HBV DNA (≥500,000 copies/ml) by PCR, n	8/14 (57)	2/4 (50)
% with HBsAg loss	1	0
Biochemical relapse (ALT>2 x ULN)		

Sustained responders Non-sustained responders	0 32 (94)	0 38 (88)
At last follow up visit		
ALT normalisation, n	17/34	16/43
% with continuing detectable HBV DNA, n	1	0
Incidence of decompensation, n (%)	2/48 (4)	4/47 (8.5)
Death, n (%)	1/48**	0/48

*sustained response is defined as patients who had persistent HBsAg loss and had less than 2 occasions with HBV DNA >100,000 copies/mL at any time during the entire post treatment follow up period.

**One patient who required open-label lamivudine for severe post treatment relapse and who developed acute duodenal ulcer bleeding completed by shock and aspiration pneumonia, died at week 64 after treatment.

Authors' conclusion:.Combination treatment of peginterferon and lamivudine has a higher sustained virological response than lamivudine monotherapy up to 3 years after treatment.

Notes:

Emtricitabine + tenofovir vs tenofovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Berg et al. tenofovir is effective alone or with emtricita	RCT multicentre Randomisation: done by a centralised randomisation	N= 105 Adefovir resistant, HBeAg positive	Inclusion: 18-69 years of age with HBeAg (+) or (-) CHB virus currently treated with ADV and showing persistent viral replication defined as HBV DNA >1000 copies/mL at screening after an ADV treatment duration of at least 24 and up to 96 weeks. ALT <10 x ULN and no evidence of decompensated liver disease (ascites, jaundice, encephalopathy, or variceal hemorrhage) or hepatocellular carcinoma or co-	Emtricitabine (200mg/day) + Tenofovir (300mg/day) (n=52) Total	Tenofovir only (300mg/day) + matching placebo (n=53)	No F/U	Primary: % with HBV DNA (<400 copies/ml) by PCR (lower limit of detection 169 copies/mL)	Gilead Sciences

bine in adefovir –treated patients with chronic hepatitis B virus infection. 2010	procedure whereby numbered bottles were assigned to patients via an interactive voice response system according to the randomisation code; stratified by history of LAM experience (<12 weeks vs >=12 weeks of LAM therapy) and HBeAg status at screening. Blinding: double-blind (patient – blinded; assessor – unclear) Patients with viraemia at week 24	or negative	infection with HIV, HCV or HDV. The patients were required to be naïve to Tenofovir and entecavir, to have not received IFN or peg-IFN within 6 months of the screening visit, and to have reported being adherent to their current ADV therapy. Prior or current LAM use (ADV and Lam combination) was allowed Setting: International multi-centre (10 in the USA, 10 in Germany, 7 in France, and 1 in Spain) Exclusion: Not stated Baseline characteristics Emtricitabine/ Tenofovir (n=52) / Tenofovir (n=53) Mean age (SD): 39 (10.4) / 40 (11.4) Male (%): 42 (80.8) / 38 (71.7) Mean HBV DNA (SD), log10 copies/ml: 5.87 (1.78) / 6.06 (1.43) Mean serum ALT (SD), I/U: 81.7 (129.9) / 58.2 (53.4) ALN above ULN (%) Yes: 26 (50) / 27 (50.9) HBeAg (+) (%): 39 (75) / 38 (72) Viral genotype (%) A: 9 (17) / 11 (21); B: 4 (8) / 6 (11)	duration of treatment: minimum 48 weeks Loss to follow up: 8 discontinued study drug and received open label emtricitabine/ tenofovir through week 48 1 of the 8 patients in the open-label emtricitabine/ tenofovir group discontinued prior to week 48 2 discontinued prior to week 48 Reasons for discontinuations for both	Total duration of treatment: minimum 48 weeks Loss to follow up: 15 discontinued double-blind study drug and received open label emtricitabine/ tenofovir through week 48 One discontinued prior to week 48		Secondary: Mean Log_{10} reduction of HBV DNA from baseline; HBV DNA undetectable (<169 copies/mL) % with ALT normalisation % with HBeAg loss % with HBeAg seroconversion (HBeAg loss and appearance of anti-HBe) HBsAg loss/ seroconversion Resistance mutations Adverse events Discontinuation	

	switched to open label combination therapy so only first 24 weeks valid comparison of randomised treatments		C D F Unable to genotype	11 (21) 21 (40) 6 (12) 1 (2)	15 (28) 18 (34) 2 (4) 1 (2)	groups were investigator's discretion, lost to F/U, withdrawal of consent in 1 patient each			due to adverse events All outcomes were assessed at week 48; some outcomes were assessed at week 24	
			Previous lamivudine treatment (%)	31 (60)	30 (57)					
			Previous IFN treatment (%)	14 (27)	10 (19)					
			Mean duration of previous ADV treatment (SD)	413.4 (183.39)	431.2 (178.5					
			Race (%) Asian Black or African American White Other	 18 (34.6) 8 (15.4) 21 (40.4) 5 (9.6)	 26 (49.1) 2 (3.8) 23 (43.4) 2 (3.8)					

Effect size

First 24 weeks of therapy	Emtricitabine + Tenofovir (n=52)	Tenofovir (n=53)	p value
Mean Log10 reduction of HBV DNA from baseline, log10 copies/ml (SD)	Not reported	Not reported	--
% with HBV DNA <400 copies/ml (SD)	36/52	35/53	--
Incidence of resistance	Not reported	Not reported	--
% with ALT normalisation	Not reported		--
% with HBeAg loss	Not reported		--

% with HBeAg seroconversion (HBeAg loss and appearance of anti-HBe)	Not reported		--
% with HBsAg loss and/or seroconversion	Not reported		--
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported		--
% withdrawn due to adverse events*	Not reported		--

*of the 105 patients randomised and treated, 80 patients completed 48 weeks of double-blind treatment without meeting the protocol-defined criteria for switch to open label emtricitabine/tenofovir.

48 weeks of therapy*	Emtricitabine + Tenofovir (n=52)	Tenofovir (n=53)	p value
Mean Log10 reduction of HBV DNA from baseline, log10 copies/ml (SD)	3.34 (1.75)	3.58 (1.29)	--
% with HBV DNA <400 copies/ml (SD)	81%	81%	0.234
Incidence of resistance	Not reported		
% with ALT normalisation	73%	67%	0.423
% with HBeAg loss	8%	8%	
% with HBeAg seroconversion (HBeAg loss and appearance of anti-HBe)	0	2% (n=1)#	--
% with HBsAg loss and/or seroconversion	Not reported		--
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported		--
% withdrawn due to adverse events*	0	0	--

*Intention-to-treat analysis was used at week 48

#male Asian patient with genotype C infection

Authors' conclusion: Tenofovir monotherapy and the combination of emtricitabine/tenofovir had similar efficacy in patients with incomplete viral suppression after therapy with ADV; response was not influenced by the presence of baseline LAM- or ADV-associated mutations. Initial monotherapy followed by combination therapy was as effective as early combination therapy.

Median adherence to the active component of the treatment regimen was similar in the 2 groups (84% in the tenofovir group and 81% in emtricitabine/tenofovir group). The % of patients with HBV DNA <400 copies/mL was higher in patients with high adherence (≥94%) than among patients with low adherence (≤68%).

Notes: patients with confirmed (within 4 weeks) plasma HBV DNA ≥400 copies/mL during double-blind treatment at week 24 or any time thereafter had the option of receiving 12 weeks of open label emtricitabine/tenofovir, which could be continued through the end of the 168-week treatment period if there was virologic response (HBV DNA<400 copies/mL). Alternatively, patients with confirmed HBV DNA ≥400 copies/mL at or any time after week 24 of double-blind treatment could discontinue the study and initiate commercially available HBV therapy rather than initiating or continuing open-label emtricitabine/tenofovir.

Additional results reported: mean reduction from baseline in ALT at week 48; virologic response according to resistance profile (ADV- or LAM- associated mutations) (genotypic analysis done at baseline).

E.6.1.6 HBeAg positive lamivudine refractory or resistant patients with CHB

Adefovir plus lamivudine versus adefovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Peters 2004	RCT- double blinded Multi centre (Australia, Canada, France, Germany,	N=58	Patients with chronic hepatitis B with compensated liver disease and lamivudine resistant hepatitis B virus (HBV). Inclusion: Patients eligible for the study were 16-65 years of age with serum hepatitis B surface antigen (HBsAg) present for at least 6 months, positive for HBeAg , and had an elevated serum ALT level (1.2-10 times	Adefovir dipivoxil 10mg once daily + ongoing lamivudine 100 mg once daily for 48 weeks (n=20) Loss to follow	Adefovir dipivoxil 10 mg once daily for 48 weeks (n=19) Lost to follow-up: 1 patient	No follow up	change in serum HBV DNA level; undetectable serum HBV DNA (by PCR, lower limit of detection 1000	Not reported

	the UK and the USA). Central randomisation.		the upper limit of normal [ULN] on at least 2 occasions 1 month apart within the preceding 6 months). All patients had received treatment with lamivudine for at least 6 months that was ongoing at the time of randomisation with confirmed HBV polymerase gene mutation within the YMDD motif by sequencing and serum HBV DNA level ≥6 $\log_{10}$ copies/ml, well preserved liver function (Child-Pugh-Turcotte score ≤7), prothrombin time <1s above ULN, albumin >3g/dL, total bilirubin <2.5g/dL, no history of variceal bleeding, ascites or encephalopathy. Exclusion: serum phosphorus ≤2.4mg/dL, creatinine ≥1.5mg/dL, creatinine clearance <50mL/min, absolute neutrophil count ≤1000 cells/mL, Hb ≤10g/dL for men or ≤9g/dl for women, serum α-fetoprotein >50ng/mL, prior use of adefovir dipivoxil or interferon or immunomodulatory therapies in previous 6 months, bephrotoxic drugs, , competitors of renal excretion and/or hepatotoxic drugs in previous 2 months or during study, prior organ transplantation, serious concurrent medical conditions (including liver disease), coinfection with HIV, alcohol or substance use, pregnancy or lactation. Baseline characteristics Characteristic / Lamivudine 100mg (n=19) / Adefovir dipivoxil 10 mg (n=19) / Adefovir dipivoxil +lamivudin (n=20) Age yr-median: 44 / 45 / 46.5 Male sex (%): 14 (74) / 17 (89) / 15 (75)	ups: 0	discontinued at week 32 due to non-compliance Lamivudine 100 mg once daily for 48 weeks (n=19) Lost to follow-up: 1 patient discontinued at week 44 due to progression of disease.		copies/mL) HBeAg seroconversion Normalisation of ALT	

			Prior lamivudine therapy-median months	24	37	29.5				
			Log $_{10}$ HBV DNA copies/ml-median	8.20	8.42	7.94				
			HBeAg (%) positive	19 (100)	19 (100)	18 (90)				
			Serum ALT-median (IU/L)	70	101	74				
			White Asian Black Other	14 (74) 5 (26) 0 0	12 (63) 7 (37) 0 0	9 (45) 9 (45) 1 (5) 1 (5)				

Effect size

Outcomes (assessed at the end of 48 weeks treatment)	Adefovir dipivoxil +lamivudine (n=20)	Adefovir dipivoxil 10 mg (n=19)	Lamivudine 100mg (n=19)	p-value
Change in serum HBV DNA level - mean±SD (95% CI)	-3.46±1.10 (-3.94, -2.97)	-4.00±1.41 (-4.65, -3.35)	-0.31±0.93 (-0.74,0.12)	P<0.001 for both comparisons versus lamivudine
Serum HBV DNA undetectable (%)(<1000 copies/ml)	7/20	5/18	0	P=0.01 for Adefovir dipivoxil vs. lamivudine; p=0.005 Adefovir dipivoxil vs. Adefovir dipivoxil +lamivudine
HBeAg negative	3/18	3/18	0/19	
HBeAg seroconversion, (%)	1/18	2/19	0/19	
Normalisation of ALT level, n/total n (%)	10/19 (53)	9/19 (47)	1/19 (5)	P=0.004 for Adefovir dipivoxil vs. lamivudine; p=0.001 Adefovir dipivoxil +lamivudine

Authors' conclusion:

In patients with compensated liver disease, adefovir dipivoxil alone or in combination with ongoing lamivudine therapy provides effective antiviral therapy in patients with lamivudine resistant HBV.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Rapti 2007	Open label RCT -no details on randomization -unclear allocation concealment	N=42	Inclusion: HbsAg positive, HBeAg negative Hep B patients with compensated liver disease (with or without histological evidence of cirrhosis) who developed genotypical HBV resistance plus virological and biochemical breakthroughs to lamivudine. Patients were required to have at screening HBV DNA ≥10^5 copies/mL within the last month before starting	Arm B: Combination: adefovir (10 mg daily) + lamivudine (dose not stated)	Arm A: Switching from lamivudine to adefovir (10 mg daily) (n=14)	24 months	1) % with undetectable HBV DNA by PCR (lower limit of detection 1000	Gilead Sciences supplied adefovir

	.		lamivudine therapy with elevated ALT values in three separate monthly occassions Exclusion: coinfected with hepatitis C or delta, or HIV, or had received liver transplantation or any antiviral drug other that IFN-a in the past. Baseline characteristics Adefovir + lamivudine (n=28) / Switching from lamivudine to adefovir (n=14) Median age (range): 56.5 (42,70) / 53 (39,76) Sex (% men): 25/28 (89.3%) / 14/14 (100%) Cirrhosis (%): 12/28 (42.9%) / 4/14 (28.5%) Median serum HBV DNA (range), log10 copies/ml: 7148150 (15500-6.4E + 08). / 1.5E+0.7 (24900-1.7E+0.8) Median serum ALT (range), U/L: 108 (52-1004) / 135 (74-608) Prior duration of lamivudine therapy (months) median (range): 30 (12-82) / 42 (12-84)	(n=28) Total duration of treatment: up to 36 months Loss to follow up/reasons: none discontinued; 2 reduced the dose of adefovir	Total duration of treatment: up to 36 months Loss to follow up/reasons: none discontinued		copies/ml) 2) Incidence of resistance 3)% with ALT normalisation (≤49IU/L)	
Effect size								

Post-treatment (assessed at 12 months treatment)	Combination: adefovir + lamivudine (n=28)	Switching from lamivudine to adefovir (n=14)	p value
% with undeectable HBV DNA (<1000 copies/mL)	68% (19/28)	78.6% (11/14)	--
Incidence of resistance*			
% with ALT normalisation (≤49IU/L)	88% (24/28)	92.9% (13/14)	--

Follow up (assessed at 24 months on treatment)	Combination: adefovir + lamivudine (n=28)	Switcing from lamivudine to adefovir (n=14)	p value
% with undetectable HBV DNA (<1000 copies/mL)	82.6% (23/28)	75% (11/14)	
Incidence of resistance*			
% with ALT normalisation (<=49IU/L)	91% (25/28)	72.7% (10/14)	

*Reported qualitatively: LAM resistant HBV mutations disappeared under adefovir monotherapy as well as under combination therapy, except in patients in combination group with suboptimal response (not achieving undetectability by PCR of HBV DNA). All patients with suboptimal response to adefovir monotherapy (n=3) had their LAM resistant HBV mutants reserved to wild type HBV (all three of them developed subsequently genotypical resistant to adefovir).

Notes: 3 of the 16 patiens with cirrhosis (all in combination group) developed hepatocelular carcinoma (HCC).

Authors' conclusion: Adding adefovir to lamivudine in HBeAg negative CHB patients with lamivudine resistance effectively suppresse HBV replication in most of them and induces biochemical remission that can be maintained in all of them at least for 3 years without any evidence of development of resistance to adefovir.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-	Outcome measures	Source of funding

						up		
Vassiliadis 2010	RCT- unclear blinding - No details on randomization, - unclear allocation concealment Pilot study: no formal power calculation	N=60	Inclusion: HBeAg negative adult Hep B patients with compensated liver disease who were receiving ongoing lamivudine therapy and had developed genotypic resistance to lamivudine (confirmed by DNA sequencing). All patients had genotype D. Exclusion: decompensated liver cirrhosis, screening calculated creatinine clearance<60 mL/min, serum phosphorus level <2.5 mg/dL, prior treatment with adefovir or other drugs against HBV (except lamivudine) within the 6 months preceding study screening, other concurrent liver diseases or other serious concurrent medical conditions, documented or suspected hepatocellular carcinoma, coinfection with hepatitis C or delta, or HIV, current alcohol or substance use and pregnancy or lactation. Baseline characteristics (see table below)	Combination: adefovir (10 mg daily) + lamivudine 100mg daily (n=45) Total duration of treatment: 12-48 months Loss to follow up/reasons: not reported	Adefovir montherapy (10 mg daily) (n=15) Total duration of treatment: 12-48 months Loss to follow up/reasons: not reported	Up to five years on treatment	1) % with undetectable HBV DNA (<400 copies/ml) 2) Incidence of resistance 3)% with ALT normalisation	Not reported

Baseline characteristics

	Adefovir + lamivudine (n=45)	adefovir (n=15)
Mean age (SD)	55 (13)	55 (10)
Sex (% men)	91.1%	86.7%
Cirrhosis (%)	19/45 (42.2%)	2/15 (13.3%)
Mean serum HBV DNA (sd), log10 copies/ml	6.2 (1.3)	6.5 (1.3)
Mean serum ALT (SD), times the	5.5 (5.4)	3.4 (3.3)

			ULN)								
			Prior lamivudine therapy (months) mean (SD)	40 (13)	41 (15)						

Effect size

Post-treatment (assessed at 12 months treatment)*	adefovir + lamivudine (n=45)	Adefovir montherapy (n=15)	p value
% with undetectable HBV DNA (<400 copies/ml)**	23/45	9/15	--
% with ALT normalisation**	32/45	7/15	--

Post-treatment (assessed at 24 months on treatment)*	adefovir + lamivudine (n=45)	Adefovir montherapy (n=15)	p value
% with undetectable HBV DNA (<400 copies/ml)	31/45	9/15	
% with ALT normalisation	39/45	8/15	-

* ITT analysis was used and data used for 12 and 24 months only as no loss to follow up before then; after then, there were losses reported overall but not reported per group.

** Figures are based on approximations as taken by a graphical presentation of results.

Authors' conclusion: Adding adefovir to lamivudine is more effective than switching to adefovir monotherapy in lamivudine resistant patients with HBeAg negative CHB.

Notes: the median follow up time was 53 months (20-60 months); 60, 60, 56, 51 and 40 patients were at risk during the first to fifth year of follow up.

E.6.1.7 HBeAg positive lamivudine refractory or resistant patients with CHB

Adefovir plus lamivudine versus lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Perrillo 2004	RCT - no details on randomization method blinding OK for group A - unclear allocation concealment ITT analysis Sample size calculation: 90 patients provided >80% power to detect a difference from 14% to 44% in the	N= 95 for Group A (randomised part of study) and N=40 for Group B	Inclusion: HBsAg positive men and women over 18 years old who were receiving ongoing lamivudine therapy for at least 6 months for CHB at the time of the screening. Patients in both groups were required to have at screening HBV DNA ≥106 copies/mL and elevated serum ALT levels >1.3 times the ULN on at least 2 occasions in previous 6 months. All patients were also confirmed to have YMDD mutant HBV. Group A: HBeAg positive Hep B patients with compensated liver disease. Group B: patients (HBeAg positive or negative) with deconmpensated liver disease or recurrent hepatitis B after liver transplantation (HBeAg positive or negative). Decompensation was defined by the presence of one or more of the following: serum bilirubin level>2 times the upper limit of normal without other cause, (2) prothrombin time>3 sec prolonged, (3) serum albumin level <32 g/L, or (4) a history of ascites, variceal hemorrhage, or hepatic encephalopathy. Exclusion: coinfected with hepatitis C or delta, or HIV, with documented or suspected hepatocellular	Group A (randomised) adefovir (10 mg) + lamivudine (100 mg once daily) (n=46) Total duration of treatment: 52 weeks Loss to follow up/reasons: 4➔ one witdrawn due to protocol violation, one withdrawn	lamivudine (100 mg once daily) + placebo (n=49) Total duration of treatment: 52 weeks 1 patient was excluded as was ineligible for the study. Loss to follow up/reasons: 2➔ one	52 weeks on treatment. No follow up	1) Log reduction of HBV DNA (Roche Amplicor assay): ≤105 copies/mL or ≥2log10 reduction from baseline 2) % with undetectable HBV DNA (lower limit of detection <200 copies/mL) 3) Incidence of resistance 4)% with ALT normalisation (<=1.0 times the ULN) 5)% with HBeAg	GlaxoSmithKline Research and Development

	HBV DNA response rates (≤105 copies/mL or ≥2log10 reduction from baseline) at weeks 48 and 52		carcinoma, anemia, leukopenia adn granulocytopenia, or thrombocytopenia or evidence of pancreatitis, previous treatment with adefovir or other drugs with activity against HBV in previous 3 months. Baseline characteristics	consent, 2 lost to follow up.	withdrew due to adverse events, one patient lost to follow up.		loss and/or seroconversion 6) HBsAg and anti-HBsAg 7) YMDD mutations 8) Adverse events	

	Group A		Gro
	Lamivudine	Adefovir +Lamivudine	
Median age (range)	42 (25-68)	43 (24-67)	53 (
No. HBeAg (+)	42 (88)	40 (87)	27 (
Sex (% men)	45 (94)	45 (98)	35 (
Median duration of prior lamivudine, months (range)	34 (4-61)	34 (10-64)	33 (
Median serum HBV DNA (range), log10 copies/ml	8.61 (4.2-10.1)	8.95 (6.6-10.1)	8.61 10.1
Mean serum ALT (SD), U/L	185 (258)	135 (148)	127

Group B (n=40): open label lamivudine and adefovir; 26 had decompensated disease and 14 were treated because of recurrent hepatitis B after liver transplantation.

Loss to follow up/reasons: 2➔ one withdrew due to adverse events, one patient lost to follow up.

Effect size in GROUP A

Post-treatment (assessed at the end of 52 weeks treatment)	adefovir (10 mg) + lamivudine (100 mg) (n=42 completers)	lamivudine (100 mg once daily) + placebo (n=46 completers)	p value
Median log reduction of HBV DNA (range)	4.6 (-1.5, 7.3)	-0.3 (-5.4, 6.0)	<=0.01
% with undetectable HBV DNA (<200 copies/mL)	9/42	0/46	<=0.01
% with ALT normalisation	14/42	3/46	P=0.002

% with HBeAg loss	6/40	1/42	--
% with HBeAg seroconversion	3/40	1/42	
% with HBsAg loss	0	0	
Incidence of resistance	26/42	44/46	p<0.001
% withdrawn due to adverse events	0/46	1/48	--

Authors' conclusion:. The addition of adefovir to lamivudine in patients with CHB with compensated or decompensated liver disease due to YMDD mutant HBV is associated with virological and biochemical improvement during 52 weeks of treatment and is well tolerated.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Perrillo 2011	Follow up study of Perrillo 2004 RCT Patients continued the same randomized treatment as Perrillo 2004 for a further 52 weeks.	N= 116 entered this follow up study (91%)	Inclusion: patients with HbsAg positive men and women over 18 years old who were receiving ongoing lamivudine therapy for at least 6 months for CHB at the time of the screening. Patients in both groups were required to have at screening HBV DNA >=106 copies/mL and elevated serum ALT levels >1.3 times the ULN on at least 2 occasions. All patients were also confirmed to have YMDD mutant HBV. Group A: HBeAg positive Hep B patients with compensated liver disease. Group B: patients with deconmpensated liver disease or recurrent hepatitis B after liver transplantation (HBeAg positive or negative). Decompensation was defined by the presence of one or more of the following: serum bilirubin level>2 times the upper limit of normal without other cause, (2) prothrombin time>2 sec prolonged, (3) serum albumin level <32	Group A adefovir (10 mg) + lamivudine (100 mg once daily) (n=38) Total duration of treatment: 52 weeks Loss to	lamivudine (100 mg once daily) + placebo (n=40) Total duration of treatment: 52 weeks Loss to	No follow up	1) Log reduction of HBV DNA (Roche Amplicor assay) 2) % with continuing detectable HBV DNA (200 copies/mL) 3) Incidence of resistance 4)% with ALT normalisation (<=1.0 times the ULN)	

			g/L, or (4) a history of ascites, variceal hemorrhage, or hepatic encephalopathy. Exclusion: coinfected with hepatitis C or delta, or HIV, with documented or suspected hepatocellular carcinoma, anemia or thrombocytopenia or evidence of pancreatitis. Baseline characteristics entering the follow up study	follow up/reasons: 3➔ 1 withdrew due to lack of compliance, 2 due to lack of efficacy.	follow up/reasons: 8➔ 1 withdrew due to adverse events, 7 for other reasons. Group B (n=38): opened label lamivudine and adefovir; 25 had decompensated disease and 13 were treated because of recurrent hepatitis B after liver transplantation. Loss to follow up/reasons: 5➔ two withdrew due to disease complications, one due to adverse events, two withdrew for other reasons.		5)% with HBeAg loss and/or seroconversion	

	Group A		Grou
	Adefovir +lamivudine	Lamivudine	
Median age (range)	42 (24-67)	42.5 (26-68)	53 (
No HBeAg (+) (%)	33 (87)	34 (85)	26 (
Sex (% men)	37 (97)	38 (95)	33 (
Median duration of prior lamivudine, months (range)	35.9 (10-64)	32.3 (4-60)	32.9
Median serum HBV DNA (range), log10 copies/ml	8.98 (6.7-10.1)	8.49 (4.2-10.1)	8.5 (10.1
Median serum ALT (range), U/L	2.78 (1.1, 40.2)	2.19 (1.0, 18.9)	1.87 16.6

Effect size in GROUP A

Post-treatment (assessed at the end of 52 weeks further treatment) –total 104 weeks treatment	adefovir (10 mg) + lamivudine (100 mg) (n=35)*	lamivudine (100 mg once daily) + placebo (n=32)**	p value

Median log reduction of HBV DNA (range)	6.18 (-0.6, 7.3)	0.11 (-2.2, 4.6)	-
% with continuing detectable HBV DNA	25/35	31/32	-
% with ALT normalisation	18/35	4/34	-
% with HBeAg loss	6/33	4/34	--
% with HBeAg seroconversion	4/33	3/34	
% with HBsAg loss	2/35	0	
Incidence of resistance	17/33	22/24	--
% withdrawn due to adverse events	0/46	1/48	--

*For patients receiving combination therapy only 1/38 had disease progression (HCC).

** In patients receiving lamivudine + placebo, 7/40 reported disease progression and they were given open label combination therapy.

Group B

Post-treatment (assessed at the end of 52 weeks further treatment) –total 104 weeks treatment	lamivudine and adefovir (n=33) overall	Subgroup analysis	
		Liver transplant before entry (n=13)*	No liver transplant be
Median log reduction of HBV DNA (range)	2.30 (2.3, 5.7)	2.72(2.3, 5.7)	2.30 (2.3, 4.8)
% with HBeAg loss	10/26	3/8	7/18
% with HBeAg seroconversion	4/26	2/8	2/18
ALT normalization	23/35		
Incidence of resistance	7/31		

* ITT analysis

Authors' conclusion:. The combination of lamivudine and adefovir for 2 years generally proved effective in lamivudine resistant cases, but there was a persistently high rate of detection of lamivudine resistant mutans and impaired virologic response in compensated patients.

Notes:

Interferon alpha plus lamivudine versus lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Akyuz et al, 2007	RCT – phase III Randomisation method: unclear Blinding: unclear Allocation concealment: unclear No sample size calculation provided Notes: patients were randomised within 6-15 months after finishing IFN alpha monotherapy.	N= 45 (39 primary non-responders and 6 relapsers)	HBeAg negative patients who were unresponsive to previous 6 months of IFN monotherapy Inclusion: HBsAg and anti-HBe positivity and HBeAg negativity for at least 18 months, HBV DNA positivity for ≥6 months, ALT elevation (at least 1.3 x ULN) for ≥3 months, biopsy proven chronic hepatitis and compensated liver disease. Setting: Turkey Exclusion: Coinfected with HCV or HDV Baseline characteristics IFN-a2b + lamivudine (n=21) / Lamivudine (n=24) Mean age (range): 41.4 (20-60) / 45.04 (25-65) Female/male, n: 4/17 / 9/15 Mean ALT (IU/L) (SEM): 179 (127.3) / 126.25 (79.3) Mean HBV: 785 (933.7) / 426.4 (549.8)	IFN a2b (10 MU, tiw, SC) plus lamivudine (100mg/day) (n=21) Total duration of treatment: IFN a2b for 6 months, plus lamivudine for another 2 years (IFN and Lamivudine were started concomitantly). Loss to follow up/reasons: 3 discontinued therapy due to adverse effects (weight loss, fever and myalgia)	Lamivudine (100mg/day) (n=24) Total duration of treatment: 2 years Loss to follow up/reasons: 2 did not attend follow up visit	No F/U	Incidence of resistance (YMDD variant were analysed at the end of treatment or when a clinical breakthrough was observed; clinical breakthrough was characterised by elevation of ALT (≥1.5 x ULN) and the reappearance of serum HBV DNA.)	Not stated

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
			DNA (pg/ml) (SEM)							
			Mean HAI (SEM)	10.2 (4.9)	9.3 (4.2)					
			Histological stage (n) 1 2 3 4	 6 5 7 3	 9 9 5 1					

Effect size

Post-treatment (at 2 years)	IFN-a2b + lamivudine (n=21)	Lamivudine (n=24)
Incidence of resistance (YMDD mutation)	10/16 (62.5%)	13/22 (59%)

Authors' conclusion:. Additional IFN-alpha therapy to LAM in HBeAg negative CHB not responding to previous IFN-alpha monotherapy does not increase the response rate compared to LAM monotherapy and does not also decrease the incidence of YMDD mutations.

Notes: Clinical breakthrough also reported in paper (different to viral breakthrough)

E.6.1.8 Combination therapies for HBeAg negative people with CHB

IFN alpha (2a/2b) + lamivudine vs lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Economou et al, 2005	RCT – multicentre open-label Randomisation method: randomised centrally using lottery cards Blinding: No Allocation concealment: unclear ITT analysis	N= 50	HBeAg negative patients (28 previously treated with IFN – 6 did not respond and 22 had relapsed after stopping treatment) Inclusion: HBsAg and anti-HBe positivity and HBeAg negativity for at least 6 months, HBV DNA >10^5 copies/mL, ALT elevation (at least 1.5 x ULN) in 3 separate monthly occasion within the last 6 months before randomisation, biopsy proven chronic hepatitis within 12 months before study entry. Setting: Greece Exclusion: Coinfected with HCV or HDV; decompensated liver disease or had previously received liver transplantation; previously treated with any AV drug other than IFN and those who had received immunosuppressive therapy within 6 months before study entry; patients with active alcohol consumption (>50g/day) or suspected hepatocellular carcinoma. Baseline characteristics	IFN a2b (5 MU, three times weekly, SC) plus lamivudine (100mg/day) (n=24) Total duration of treatment: 24 months Loss to follow up/reasons: 3 by 10th week (2 had hematologic toxicity; 1 had exacerbation of liver disease)	Lamivudine (100mg/day) (n=26) Total duration of treatment: 24 months Loss to follow up/reasons: 0	24 months on treatment plus 6 months follow up	Undetectable HBV DNA (<400 copies/mL [lower limit of detection]) ALT normalisation Incidence of resistance (YMDD mutation)	Not stated

	IFN-a2b + lamivudine (n=24)	Lamivudine (n=26)
Median age (IQR)	53 (47-60)	58 (41-66)
Male, n (%)	15/24 (63)	18/26 (69)
Median ALT (IU/L) (IQR)	79 (57-100)	59 (52-94)
Median log10 HBV DNA (IQR)	6.1 (5.2-7.2)	5.9 (5.2-6.6)
Previous IFN-alpha therapy, n (%)	13/24 (54)	15/26 (58)
Cirrhosis *	11/24 (45.8)	13/26 (50)

*Ishak, fibrosis 5 or 6

Effect size

At 24 months treatment	IFN-a2b + lamivudine (n=24)	Lamivudine (n=26)
Undetectable HBV DNA, n (%)	18/21 (86)	13/26 (50)
ALT normalisation, n (%)	19/21 (90)	16/26 (62)
Virological breakthrough	3/21	11/24
Discontinued IFN due to adverse events, n	3/24	0/26
At 30 months (or 6 months post treatment follow up)		
Undetectable HBV DNA (ITT)	4/21 (21)	3/26 (12)
ALT normalisation, n (%)	6/21 (28)	5/26 (19)
Incidence of resistance (YMDD mutation)	2/21 (10)	12/26 (46)

Authors' conclusion:. IFN-alpha plus lamivudine combination therapy does not increase the sustained response, compared to lamivudine. However, combination therapy reduces the likelihood of virologic breakthrough due to YMDD mutant and prolongs the time period until the breakthrough development.

Notes: other reported outcomes – sustained virologic response, biochemical breakthrough, complete response

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yurdaydin et al, 2005	RCT Randomisation method: unclear Blinding: unclear Allocation concealment: allocation sequence was generally centrally at the dept Gastroenterology of the University of	N= 78	HBeAg negative patients Inclusion: CHB patients who were HBeAg (-) and anti HBeAg positive, had to have detectable HBV DNA levels by a molecular hybridisation assay within 1 month before study started; ALT ≥1.3-10 x ULN on 2 occasions. They had to have a liver biopsy done within 1 year of study entry and all had HAI of ≥3 (Knodell); no previous use of interferon in last 6 months. Setting: University of Ankara Medical School and the Dept Gastroenterology of a hospital in Ankara (2 centres) Exclusion: coinfected with HCV/HDV/HIV; albumin below 3.5g, bilirubin >2mg/dl, increased prothrombin time >3s above normal, white blood and platelet counts of <3000 and 100,000 mm^3; significant disease which might have interfered	Lamivudine was given alone for the first 2 months. Lamivudine in combination with IFN a2a (9MU, three times weekly) for another 10 months (n=39) Total duration of treatment: 52 weeks Loss to follow up/reasons: 2,	Lamivudine monotherapy (100mg/day) (n=39) Total duration of treatment: 52 weeks Loss to follow up/reasons: 2 one had	6 months (short term) and a median of 27 months (long term)	% with undetectable HBV DNA using hybridisation assay (<5 pg/mL [lower limit of detection]) Reduction in HBV DNA (median; real-time PCR) % with ALT normalisation Incidence of resistance	Not stated

	Ankara Medical School No sample size calculation provided		with the conduct of the study; previous us eof nucleoside analogue Baseline characteristics IFN-a2a+ lamivudine (n=39) / Lamivudine (n=39) Mean age ±SD (range): 41.1±9.9 (19-68) / 43.1±9.3 (17-61) Sex, M/F (% male): 29/10 (74.4) / 28/11 (71.8) Prior use of IFN (%): 4 (10.3) / 7 (17.9) Mean ALT ± SD: 123.9 ±83.7 / 121.8 ± 80.9 ALT (%) Normal: 2 / 0 <2ULN: 12 (30.8) / 10 (25.6) ≥2 ULN: 27 (69.2) / 29 (74.4) HBV DNA (pg/mL)±SD: 371.6±627.6 / 273.1±560.2 Cirrhosis: 5 / 6 Previous IFN therapy n (%): 4 (10.3) / 7 (17.9)	one discontinued IFN due to side effects and one discontinued treatment due to private problems. Notes: 2 patients reduced IFN dose (to 5MU) due to subjective complaints	hepatocellular carcinoma in the 8th month of treatment and had a lobectomy; another patient was withdrawn due to protocol violation (prescreening HBV DNA were PCR based and qualitative). During 6 month follow up, one refused to stop LAM and another did not come for F/U visit.		(YMDD mutation) Histologic improvement	

Effect size

At the end of 1y treatment	IFN-alpha + lamivudine (n=39)	Lamivudine (n=39)
% with undetectable HBV DNA (<5 pg/mL)	36/39 (92.3%)	35/39 (89.7%)
% with ALT normalisation	20/39 (51.3)	26/39 (66.7)

Virological breakthrough	1/39	2/39
Median reduction in HBV DNA (real time PCR), log copies/ml	1.785 x 106 (From 1.8 x 106 to 1.5 x 104)	1.88 x 106 (From 1.9 x 106 to 2 x 104)
Incidence of resistance - YMDD mutation (%)*	8/33	17/32
Histologic improvement (definition unclear)	17/25	19/25

*Most of the patients had a mixed population of YMDD variants and wild type YMDD (24/25; 96%)

6 months follow up	IFN-alpha + lamivudine (n=39)	Lamivudine (n=39)
% with undetectable HBV DNA (<5 pg/mL)	21/39 (53.8)	23/39 (59.0)
% with ALT normalisation	20/39 (51.3)	16/39 (41)

A median of 27 months follow up (range 21-36 months)	IFN-alpha + lamivudine (n=36)	Lamivudine (n=34)
% with undetectable HBV DNA (<5 pg/mL)	9/36 (25)	9/34 (26.5)
% with ALT normalisation	9/36 (25)	7/34 (20.6)

Authors' conclusion:. Efficacy of combination treatment is similar to lamivudine monotherapy. However, combination treatment decreases the development of YMDD mutation strains compared with lamivudine monotherapy.

Notes:

Reference	Study type	Number of	Patient characteristics	Intervention	Comparison	Length of	Outcome measures	Source of

		patients				follow-up		funding
Akarca et al, 2004	RCT – Randomisation method: using the random between function of Microsoft Excel software, without being subjected to stratification, and divided into two groups. Random allocation rule was applied (each selected number was dropped from the number list and never selected again) Blinding:	N= 80	HBeAg negative patients Inclusion: HBsAg positive and anti-HBe positive and HBeAg negative for at least 6 months before treatment; HBV DNA >5pg/mL at least 1 month before enrolment; ALT >1.5 x ULN at two measurements at least 1 month apart; had a liver biopsy performed within the year before study entry; white cell count >4000/mm^3; platelet >100,000/mm^3; negative for hereditary diseases Setting: single centre, Turkey Exclusion: other causes of liver disease, coinfected with HCV, HDV or HIV; decompensated liver disease; subjects with anti-nuclear antibodies level of >1/160 or alpha-fetoprotein levels of over 20ng/ml; renal insufficiency; uncontrolled diabetes and cardiac disease; serious psychiatric problems; patients that were consuming >20g of alcohol/day, receiving alternative medicines, using immunosuppressive therapy or corticosteroids; had received IFN during the past one year, had taken lamivudine or NAs any time before the study Baseline characteristics IFN + lamivudine (n=40) / Lamivudine (n=40) Mean age ±SD: 42 ±10 / 43 ±12	Lamivudine (150mg/day) for 96 weeks, plus IFN (9-10MU, three times weekly) for 24 weeks (1st 6 months of treatment)* (n=40) Total duration of treatment: 96 weeks (combination therapy for 24 weeks) Loss to follow up/reasons: 0 *due to the small size of the study pop (<200), in order to have the groups of equal sizes, random allocation rule was applied to randomise the patients	Lamivudine monotherapy (150mg/day) NB not standard dose (n=40) Total duration of treatment: 96 weeks Loss to follow up/reasons: 0	96 weeks	% with undetectable HBV DNA using hybridisation method (<10^5 copies/mL) % with ALT normalisation HBsAg loss Histological improvement	Not stated

	unclear Allocation concealment : unclear 40 patients per group needed for p=0.05 and power = 80% to detect a difference of 20% in end of therapy response between groups (80% vs 60%)		<table><tr><td>M/F</td><td>30/10</td><td>29/11</td></tr><tr><td>Mean ALT ± SD</td><td>163±77</td><td>161±87</td></tr><tr><td>Median HBV DNA (pg/mL) (range)</td><td>114.5 (7-2000<)</td><td>114 (5-2000<)</td></tr><tr><td>Necro-inflammatory activity (mean ± SD)</td><td>8.2 ± 3.6</td><td>9.2 ± 3.9</td></tr><tr><td>Fibrosis (mean ± SD)</td><td>2.6 ± 1.2</td><td>2.2 ± 1.3</td></tr><tr><td>Prior interferon treatment, n</td><td>20**</td><td>17*</td></tr></table>*Of the 17 patients in the LAM group had received previous IFN treatment, 6 patients had relapsed after a response to IFN treatment. **Of the 20 patients in the combined group had received previous IFN treatment, 7 had relapsed despite a response at end of treatment. There was no difference between the groups in terms of previous IFN therapy.					

Effect size

At 24 weeks (end of combination phase of treatment)	IFN + lamivudine (n=40)	Lamivudine (n=40)
Mean (SD) ALT	58 (37)	36 (21)
% with undetectable HBV DNA *	34/40 (85%)	37/40 (92.5%)
% with ALT normalisation, n (%)	17/40	30/40

At 96 weeks (end of treatment)	IFN + lamivudine (n=40)	Lamivudine (n=40)
Mean (SD) ALT	29 (26)	28 (15)
% with undetectable HBV DNA *	39/40 (97.5%)	36/40 (90%)
% with ALT normalisation, n (%)	32/40 (80)	33/40 (82)
HBsAg loss	0 (0)	0 (0)
Discontinued study drugs (IFN) due to adverse events, n (%)	1 (2.5)**	0(0)

*HBV DNA measured by hybridisation method

**One patient stopped IFN treatment due to fatigue and weakness

Authors' conclusion:.Addition of IFN to the lamivudine regimen does not increase the effectiveness of the treatment. Considering the side effects of IFN treatment, this combination seems not to be convenient for anti-HBe-positive CHB.

Notes: other outcomes reported in paper - % with histologic improvement by 2 points or more (result given before and after treatment, not given by group); breakthrough (phenotypic resistance) defined as an increase in ALT together with HBV DNA positivity despite the continuing treatment (n=3 in lamivudine group). YMDD mutations were not assessed in this study.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Santantonio et al, 2002	RCT Randomisation method: unclear	N= 50	HBeAg negative (anti-HBe positive) patients (21 previously treated with IFN: 7 no response and 14 relapsed after stopping) Inclusion: had a liver biopsy showing active disease within 24 months before study entry,	Lamivudine 100mg daily in combination with IFN (5MU, three times weekly) (n=24)	Lamivudine monotherapy (100mg/day)	12 months of treatment plus at least	% with undetectable HBV DNA using PCR (<400 copies/mL and	No funding from the pharma

	Blinding: unclear Allocation concealment: unclear No sample size calculation provided		positive for HBV DNA by molecular hybridisation and had elevated ALT levels. Setting: Italy Exclusion: decompensated cirrhosis, HCV/HDV/HIV Baseline characteristics IFN + lamivudine (n=24) / Lamivudine (n=26) Mean age ±SD (range): 47 ±7 (31-57) / 44 ±11 (25-63) Sex, M/F: 19/5 / 22/4 Prior use of IFN (%): 11 (46) / 10 (38) Mean ALT ± SD: 224 ±175 / 272 ± 358 HBV DNA (pg/mL)±SD: 235±446 / 242±317 Cirrhosis (n): 7 / 9	Total duration of treatment: 1 year Loss to follow up/reasons: 0 In one patient, IFN dose reduction was required for thrombocytopenia	(n=26) Total duration of treatment: 1 year Loss to follow up/reasons: 0	6 months (range 6-13 months)	hybridisation with a 5pg/ml lower limit of detection) % with ALT normalisation Incidence of resistance (YMDD mutation)	ceutical ompany involved with the study drugs.

Effect size

At the end of 1y treatment	IFN+ lamivudine (n=24)	Lamivudine (n=26)
% with undetectable HBV DNA by PCR (<400 copies/ml)	21/24	11/21
% with ALT normalisation	21/24	24/26

Incidence of resistance - YMDD mutation	0	5

Authors' conclusion: In anti-HBe positive chronic hepatitis B, a 12 month course of LAM/IFN combination therapy is as beneficial as LAM monotherapy. After therapy discontinuation, most patients relapsed; the combination regimen appeared to prevent or delay the emergence of YMDD variants.

Notes: ALT flare post treatment and end of treatment response (definition unclear) were reported; subgroup analysis (N=17) of HBV DNA detected by quantitative PCR

Lamivudine + IFN a v lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Scotto et al, 2006	RCT – Randomisationmethod: unclear Blinding: unclear Allocation concealment: unclear No sample size calculation provided	N= 59	Patients with (HBeAg negative) chronic anti-HBe positive hepatitis B and precore-mutant variants. Previous non-responders to 2 or 3 cycles of IFN-alpha therapy. The last cycle was completed ≥ 6 months before starting the present study. Inclusion: serum ALT>2 x ULN for >6months; HBV infection based on the presence of HBsAg in the serum, and HBV DNA positivity >5 pg/ml, determined by sandwich hybridisation testing); positive histology for chronic hepatitis. Cirrhosis within 6 months of the study according to the Knodell-Ishak classification (HAI ave. score ~13) Setting: Italy Exclusion: other causes of chronic hepatitis (HCV,	Lamivudine (100mg/day) plus IFN-alpha (6MU, three times weekly) (n=20) Also switching: received the same combination for 40 weeks after pre-treatment with lamivudine for 12 weeks (n=18)	Lamivudine monotherapy (100mg/day) (n=21) Total duration of treatment: 52 weeks Loss to follow up/reasons: 0	52 weeks post treatment	% with continuing detectable HBV DNA using hybridisation method (≥5pg/mL) % with ALT normalisation HBsAg loss Discontinued study drug due to adverse events	Not stated

	ITT analysis (therapeutic safety was analysed according to treatment received for all patients who were given at least one dose of study medication – "as treated population")		HDV, autoimmunity, alcoholism, Wilson's disease, hemochromatosis, alpha1-antitrypsin deficiency); past or present episodes of hepatic failure, a positive test for HIV and drug addiction. Baseline characteristics	Total duration of treatment: 52 weeks Loss to follow up/reasons: 0			Histologic improvement (a reduction of ≥ 2 points in the necroinflammatory score*) Incidence of resistance (measured by YMDD mutations)	

	IFN alpha + lamivudine (n=20)	Lamivudine (n=21)	LAM followed combine therapy (n=18)
Mean age (range)	42 (23-61)	44 (27-63)	45 (26-6
M/F	10/10	10/11	12/6
Mean ALT ± SD (U/L)	313 (126-389)	279 (112-357)	256 (99-
Mean HBV DNA (pg/mL) (range)	714 (202-1009)	675 (212-975)	763 (276 885)
Cirrhosis, n	2	2	3

Effect size

At 52 weeks (end of treatment)	IFN-alpha + lamivudine (n=20)	Lamivudine (n=21)	Lamivudine followed by combined therapy (n=18)
% with continuing detectable HBV DNA (≥5pg/mL)	6/20 (30)	7/21 (33.3)	5/8 (27.8)
% with ALT normalisation, n (%)	14/20 (70)	13/21 (61.9)	13/18 (72.2)
YMDD mutations, n	1/20	2/21	0/4? (check)

Discontinued study drugs (IFN) due to adverse events, n	2/20	3/21	2/18

At 52 weeks follow up	IFN-alpha + lamivudine (n=20)	Lamivudine (n=21)	Lamivudine followed by combined therapy (n=18)
% with continuing detectable HBV DNA (≥5pg/mL)	13/20 (65)	14/21 (66.7)	12/18 (66.7)
% with ALT normalisation or sustained biochemical response, n (%)	7/20 (35)	7/21 (33.3)	6/18 (33.3)
HBsAg loss	0 (0)	0 (0)	0 (0)
Histologic improvement (a reduction of ≥ 2 points in the necroinflammatory score*), n (%)	6/20 (30)	5/21 (23.8)	5/18 (27.7)

*Fibrosis was improved in the same patients who demonstrated a reduction of ≥2 points in the necro-inflammatory score.

Authors' conclusion:.A 12 month course of LAM/IFN combination therapy is as beneficial as LAM monotherapy and also that combination therapy for 40 weeks after 12 week pre-treatment with lamivudine does not increase the rate of sustained response. Combination therapy seems more effective in preventing the emergence of YMDD variants, but this potential benefit should be further investigated in other studies.

Notes:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yuki et al, 2008	RCT Randomisation method: not stated Blinding: liver biopsy blinded Allocation concealment: not stated No sample size calculation provided	N=64	Japanese patients with perinatally transmitted Hep B virus genotype C (difficult to treat population with relatively high viral replication) Mixed HBeAg positive (41/64 [64%]) and negative (36%) population, with 13% previously treated with IFN Inclusion: Japanese patients with CHB, positive for HBsAg, fluctuating ALT levels Setting: Japan Exclusion: decompensated cirrhosis, hepatocellular catrcinoma, alcohol abuse, automimmune liver disease, markers for hepatitis C or D or HIV infection Baseline characteristics IFN-alpha + lamivudine (n=30) / Lamivudine (n=34) Median age (range): 39 (24-66) / 48 (24-66) Male, n (%): 25 (83) / 27 (79) Prior use of IFN: 3 (10) / 5 (15)	IFN-alpha 6 million units daily, for 2 weeks, then 3 times weekly plus 100mg/day lamivudine for 24 weeks; followed by lamivudine alone for 28 weeks (n=30) Total duration of treatment: 52 weeks Loss to follow up/reasons: 0	Lamivudine monotherapy (100mg/day) (n=34) Total duration of treatment: 52 weeks Loss to follow up/reasons: 0	No F/U (end of 52 weeks treatment)	Undetectable HBV DNA (by PCR kit, lower limit of detection 2.6 log copies/mL; upper limit of detection 7.6 log copies/mL; arbitrary values of 2 and 8 log copies per mL were attributed to samples with HBV DNA levels <2.6 and >7.6log copies/mL respectively) % with ALT normalisation % with HBeAg seroconversion Incidence of resistance	Not stated

			n (%)						(YMDD mutation) Histologic improvement (a reduction of at least 2 points in the necroinflammatory score and at least one point in the fibrosis score)	
			Median ALT level, IU/L (range)	90 (25-1195)	76 (30-1545)					
			HBeAg positive (%)	23 (77)	18 (53)					
			HBV DNA (log copies/mL)	7.5 (3 to>7.6)	7.0 (3.9 to >7.6)					
			Genotype C (%)	30 (100)	34 (100)					
			Histology Necro-inflammatory score Fibrosis score	8 (2-13) 3 (1-4)	7 (2-11) 3 (0-4)					

Effect size

At the end of 52 week treatment	IFN-alpha + lamivudine* (n=30)	Lamivudine (n=34)	Comparison
Undetectable HBV DNA (<2.6 log copies/mL)	20/30 (67%)	19/34 (56%)	p=0.106
% with ALT normalisation	26/30 (87)	18/34 (53)	p=0.006
HBeAg seroconversion (%)	6 (26)	2 (11)	p=0.429
Incidence of resistance - YMDD mutation (%) (excluding 8 PCR-negative patients – 4 in each group)	2/26 (8)	9/30 (30)	p=0.047
Histologic improvement (in 52 patients with paired biopsies) Necroinflammatory score reduced at least 2 points Fibrosis score reduced at least one point	 26/29 (90%) 9/29 (31)	17/23 (74%) 10/23 (43)	 p=0.161 p=0.397

*Combination treatment duration was 24 weeks, followed by lamivudine monotherapy for additional 28 weeks.

Authors' conclusion: Simultaneous commencement of treatment with IFN and a nucleoside analog may be worthy as a treatment option to augment the early virologic response and prevent drug resistance in difficult to treat patients. Combination treatment was also shown to enhance reversion of the precore mutation.

Notes: Posttreatment follow up results not extracted due to the small no. patients assessed (N<5)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Montazeri et al, 2005	RCT Randomisationmethod: unclear Blinding: unclear Allocation concealment: allocation sequence was generally centrally at the dept Gastroenterology of the University of Ankara Medical School No sample size calculation provided	N= 78	HBeAg positive and negative patients (non-responsive to previous IFN therapy) Inclusion: CHB patients who were HBeAg (-), had to have detectable HBV DNA levels byb a molecular hybridisation assay within 1 month before study started; ALT ≥1.3-10 x ULN on 2 occasions. They had to have a liver biopsy done within 1 year of study entry and all had HAI of ≥3 (Knodell). Setting: Iran Exclusion: coinfected with HCV/HDV/HIV; albumin below 3.5g, bilirubin >2mg/dl, increased prothrombin time >3x above normal, white blood and platelet counts of <3000 and 100,000 mm3. Baseline characteristics IFN-a2a+ lamivudine (n=39) / Lamivudine (n=39) Mean age ±SD (range): 41.1±9.9 (19-68) / 43.1±9.3 (17-61) Sex, M/F (% male): 29/10 (74.4) / 28/11 (71.8) Prior use of IFN: 4 (10.3) / 7 (17.9)	Lamivudine was given alone for the first 2 months. Lamivudine in combination with IFN a2a (9MU, three times weekly) for another 10 months (n=39) Total duration of treatment: 52 weeks Loss to follow up/reasons: 2, one discontinued IFN due to side effects and one discontinued treatment due to private problems.	Lamivudine monotherapy (100mg/day) (n=39) Total duration of treatment: 52 weeks Loss to follow up/reasons: 2 one had hepatocellular carcinoma in the 8th month of treatment and had a lobectomy; another	6 months (short term) and a median of 27 months (long term)	% with continuing detectable HBV DNA using hybridisation assay (≥5 pg/mL) Reduction in HBV DNA (median; real-time PCR) % with ALT normalisation Incidence of resistance (YMDD mutation) Histologic improvement	Not stated

			(%)			Notes: 2 patients reduced IFN dose (to 5MU) due to subjective complaints	patient was withdrawn due to protocol violation (prescreening HBV DNA were PCR based and qualitative). During 6 month follow up, one refused to stop LAM and another did not come for F/U visit.			
			Mean ALT ± SD ALT (%) Normal <2ULN ≥2 ULN	123.9 ±83.7 2 12 (30.8) 27 (69.2)	121.8 ± 80.9 0 10 (25.6) 29 (74.4)					
			HBV DNA (pg/mL)±SD	371.6±627.6	273.1±560.2					
			Cirrhosis	5	6					

Effect size

At the end of 1y treatment	IFN-alpha + lamivudine (n=39)	Lamivudine (n=39)
% with continuing detectable HBV DNA (≥5 pg/mL)	13 (7.7)	4 (10.3)
% with ALT normalisation	20/39 (51.3)	26/39 (66.7)
Median reduction in HBV DNA (real time PCR), log copies/ml	1.785 x 106 (From 1.8 x 106 to 1.5 x 104)	1.88 x 106 (From 1.9 x 106 to 2 x 104)
Incidence of resistance - YMDD mutation (%)*	8/33	17/32
Histologic improvement (definition unclear)	17	19

*Most of the patients had a mixed population of YMDD variants and wild type YMDD (24/25; 96%)

6 months follow up	IFN-alpha + lamivudine (n=39)	Lamivudine (n=39)
% with continuing detectable HBV DNA (≥5 pg/mL)	18/39 (46.2)	16/39 (41)
% with ALT normalisation	20/39 (51.3)	16/39 (41)

A median of 27 months follow up (range 21-36 months)	IFN-alpha + lamivudine (n=36)	Lamivudine (n=34)
% with continuing detectable HBV DNA (≥5 pg/mL)	27/36 (75)	25/34 (73.5)
% with ALT normalisation	9/36 (25)	7/34 (20.6)

Authors' conclusion:. Efficacy of combination treatment is similar to lamivudine monotherapy. However, combination treatment decreases the development of YMDD mutation strains compared with lamivudine monotherapy.

Notes:

INF a 2a + Lamivudune vs INF a 2a

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Karabay et al, 2005	RCT Randomisatio	N= 27	HBeAg negative patients (treatment naïve) Inclusion: Positive HBsAg and anti-HBe for ≥6	IFN-a2a 9 million units 3 times weekly in	IFN-a2a 9 million units	6 months post	HBeAg seroconversion	Not stated

	nmethod: unclear Randomised in 1:1 ratio Blinding: unclear Allocation concealment: unclear		months; serum HBV DNA >105 copies/mL; serum ALT >2 x ULN; liver biopsy showing chronic hepatitis. Setting: Turkey Exclusion: history of allergy to IFN-alpha or lamivudine; psychiatric illness; decompensated cirrhosis; pregnancy; breast-feeding; age <17 or >65y. Positive result for any HBeAg, HDV, HIV or HCV; patients with a history of AV drug or IFN-alpha use. Baseline characteristics IFN-a2a + lamivudine (n=14) / IFN-a2a (n=13) Mean age (range): 41 (19-55) / 37 (23-58) Male/ female: 7/7 / 5/8 Mean Knodell inflammatory score: 8 / 9 ALT (x normal range): 2.4 (2.0-5.8) / 2.1 (2.0-6.2)	combination with 100mg/day lamivudine (n=14) Total duration of treatment: 1 year starting at the time of initiation of IFN-a treatment Loss to follow up/reasons: 0	3 times weekly alone (n=13) Total duration of treatment: 24 weeks (6 months) Loss to follow up/reasons: 0	treatment		

Effect size

At end of 6 months follow up	IFN-a2a + lamivudine (n=14)	IFN-a2a (n=13)
HBeAg seroconversion	0	0

Authors' conclusion:.The results of this study indicate that IFN-alpha monotherapy for the treatment of HBeAg negative patients is effective and that the addition of lamivudine does not result in superior efficacy in the treatment of HBeAg negative patients with CHB. The author listed several study limitations, which include early termination of the study due to the limited number of cases that met the following requirement - recent guidelines suggested that HBeAg negative patients should be treated with IFN-a for at least 1 year; liver histology after treatment was available for only 4 patients; sustained response was determined for up to 12 months post-treatment for IFNa monotherapy group, but at 6 months post-treatment for the combination group. Therefore, the comparative efficacy of the combination therapy could only be assessed for up to 6 months.

Notes:

Peg INFa 2b + LAM v Peg INF a 2b

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Papadopoulos 2009	Randomised open label study Randomisation was not controlled and no stratification process was followed. No	N=126 randomised .	Patients with hepatitis B e antigen (HBeAg) negative chronic hepatitis B. Inclusion: Laboratory test results that were negative for HBeAg and positive for both HBsAg and antiHBe antibody for at least 6 months before the initiation of the study, HBV DNA > 10^5 copies/ml, alanine aminotransferase levels 1 to 10 times greater than the upper limit of the normal range (>30 IU/ml in men and >19 IU/ml in women), histologic evidence of necroinflammatory activity in a liver biopsy specimen and signs of chronic hepatitis.	Pegylated interferon alfa-2b ≥1.5 µg/kg once daily + lamivudine 100 mg once daily for 48 weeks (n=90). 2 withdrew from treatment during the	Pegylated interferon alfa-2b ≥1.5 µg/kg once daily for 48 weeks (n=36). 1 withdrew from treatment during the first month because of	Week 72 (24 weeks follow-up after 48 weeks of treatment)	Primary endpoints: Virological response defined as undetectable level of HBV DNA with the lowest limit of detection <60 IU/ml at week 72. Biochemical response defined as	Departmental sources of the authors

	blinding. Sample size calculation shown: 80% power to detect a 30% absolute difference at p=0.05 with 85 patients in combination arm and 34 in monotherapy		Exclusion: Patients with decompensated liver disease; a comorbid condition, including a psychiatric illness; neutropenia (<1500 cells/µl); thrombocytopenia (<100,000 cells/µl); creatinine level of >1.5 x upper limit of the normal range; a history of alcohol or drug abuse; or co-infection with the hepatitis C virus, the HIV virus or the hepatitis D virus were excluded from the study. Baseline characteristics characteristic: Pegylated interferon alfa-2b +lamivudine (n=88) [group A] / Pegylated interferon alfa-2b patients (n=35)[group B] Sex (men: women): 65:23 / 30:5 Age (yr): 46.7 / 46.3 Necro inflammatory activity score: 8.90 / 6.04 (p<0.0001) Fibrosis score: 2.13 / 1.43 (p<0.0001) HBV DNA $\log_{10}$ copies/ml: 5.78 / 6.16 (p=0.008) Alanine aminotransferase (IU/ml): 135.7 / 96.5 (p=0.015)	first month because of adverse events; n=88 analysed	adverse events; 35 analysed		normalisation of alanine aminotransferase levels(≤ 30 IU/ml in men and ≤19 IU/ml in women at week 72 Secondary endpoints: Virologic response at the conclusion of treatment (Week 48) Mean decrease in HBV DNA and alanine aminotransferase levels at weeks 48 and 72.	
Effect size								

outcome	Pegylated interferon alfa-2b +lamivudine (n=88)	Pegylated interferon alfa-2b patients (n=35)	p-value
End of treatment (At week 48)			
Virological response: undetectable HBV DNA (<60IU/mL)	73/88 (83%)	24/35 (68.6)%	P=0.079
Mean HBV DNA levels log $_{10}$ copies/mL	3.27	2.91	P=0.0006
Alanine aminotransferase levels (IU/ml)	38.5	36.9	
End of follow-up (Week 72)			
Virological response	52/88 (59.1%)	15/35 (42.9%)	P=0.104
Biochemical response	24/88 (27.3%)	14/35 (40%)	P=0.170
Mean HBV DNA levels log $_{10}$ copies/mL	4.04	3.58	Not reported
Alanine aminotransferase levels (IU/ml)	52.6	51.8	Not reported

Multiple regression analysis:

The virologic response at the conclusion of follow-up (week 72) was independently correlated with pegylated interferon alfa-2b dose (p=0.001), and the biochemical response at the conclusion of follow-up was independently co-related with necroinflammatory activity (p=0.041), the pegylated interferon alfa-2b dose (p=0.046), and lamivudine treatment (p=0.038).

Authors' conclusion:

The results supported the use of pegylated interferon alfa-2b in patients with HBeAg negative chronic hepatitis B; however the concomitant use of lamivudine produced no additional clinical benefit.

PegINF alpha 2b + Lamivudine vs PegINF alpha 2b

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kaymakoglu 2007	RCT	N=48	Patients with hepatitis B virus E antigen negative chronic hepatitis B.	Pegylated interferon	Pegylated interferon	Week 72 (24 weeks	Virological response- HBV	None reported

	Open label. Details of randomisation and allocation concealment not reported.		Inclusion: 18 years and older; Hepatitis B surface antigen (HBsAg) positivity for at least 6 months, HBeAg negativity and anti-HBe positivity on two occasions in the past 3 months, serum alanine amino transferase levels >1.3 times the upper limit of normal on two occasions during the preceding 3 months, HBV DNA positivity (lower limit of detection, 4 pg/ml), and compensated liver disease with histological evidence of chronic hepatitis. Exclusion: Patients were excluded from participation in the study if they exhibited any other cause of chronic liver disease, received immunosuppressive or antiviral treatment in the previous 6 months, or exhibited hepatocellular carcinoma. Baseline characteristics (see table below)	(PEG-IFN) alfa-2b at 1.5µg/kg of body weight/ week +lamivudine 100 mg/day for 48 weeks (n=29) Early withdrawal: 2	(PEG-IFN) alfa-2b at 1.5µg/kg of body weight/week for 48 weeks (n=19). Early withdrawal: 3	after the end of 48 weeks of treatment)	DNA level by hybridization assay (lower limit of detection 4pg/mL) and by PCR at end of follow up (lower limit of detection 400 copies/mL) Biochemical response- ALT level normalisation	

Characteristic	PEG-IFN alfa-2b (n=19)	PEG-IFN alfa-2b+lamivudine (n=29)
Gender Male female	 13 6	 20 9
Age (yr)	42.6±10.9	43±7.8
ALT (IU/litre)	130.4±45	161.5±127.4
Total bilirubin (mg/dl)	0.8±0.4	0.8±0.4

			Albumin g/dL	4.3±0.3	4.5±0.7					
			HBV DNA (pg/ml)	182.3±175.4	209.6±207.8					
			HAI	7.0±3.2	8.3±2.9					

Effect size

Outcomes	PEG-IFN alfa -2b (n=19)	PEG-IFN alfa-2b +lamivudine (n=29)	p-v
Biochemical (ALT level normalisation)			
End of treatment (week 48)	10 (53)	19 (66)	Nc re
End of follow-up (week 72)	8/16	14/27	Nc re
Virological			
HBV DNA level <4 pg/ml End of treatment (week 48)	12 (63)	23 (79)	Nc re
HBV DNA level <4 pg/ml End of follow-up (week 72)	7/16	10/27	Nc re
HBV DNA level <400 copies /ml (week 72)	5/16	7/27	Nc re
HBsAg seroconversion at week 72	2/16	1/27	

:

Multivariate analysis:

Multivariate analysis showed that the only variable influencing the end-of follow-up response was female sex ($p<0.05$).

Adverse effects:

The most frequent treatment-related adverse effects in all patients were flu-like symptoms (71%), cytopenia (23%), injection site reactions (10%), pruritus (8%), depression (6%) and thyroiditis (2%). No serious adverse events were reported and no patient discontinued treatment due to an adverse event.

Authors' conclusion:

The results of this study that PEG-IFN alfa-2b monotherapy and PEG-IFN alfa-2b +lamivudine provide similar therapeutic outcomes in HBeAg-negative patients with hepatitis B. In both treatment arms the proportions of patients who had serum alanine amino transferase normalisation and HBV DNA negativity at the end of treatment and at end of follow-up were similar.

Pegylated interferon alpha-2a plus adefovir versus pegylated interferon alpha-2a

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Piccolo et al, 2009	RCT – multi centre Randomisation method: centrally randomised; computer generated Blinding: unclear Allocation concealment: study drug assignment was sent via	N= 60	HBeAg negative patients (mixed population of previously treated and treatment naïve patients) Inclusion: at least 18 years of age with biopsy proven HBeAg-negative CHB (HBsAg positive for at least 6 months, increased ALT (> ULN, <10 x ULN on at least 2 occasions in last 6 months), HBV DNA >2000IU/mL, a histological diagnosis of CHB within the preceding 24 months. Setting: outpatient hepatology/ infectious disease clinics, Italy Exclusion: presence of clinical signs of cirrhosis, coinfection with HCV, HDV or HIV, chronic liver disease of other aetiology, pregnancy or lactation, creatinine levels>1.5 x ULN, neutrophil count <1500 cells/mm^3, platelet count <90,000	Peg-IFN-alpha2a 180 µg/week plus adefovir 10mg/day (n=30) Total duration of treatment: 48 weeks Loss to follow up/reasons: 5 (4 due to adverse events, 1 non-compliance) NOTE: all patients who	Peg-IFN-a2a 180 µg/week (n=30) Total duration of treatment: 48 weeks Loss to follow up/reasons: 5(4 due to adverse events, 1 non-compliance)	48 weeks of treatment + 24 weeks post treatment	Primary: % with undetectable HBV DNA (<2000IU/ml [3.3 $\log_{10}$ IU/mL]) at week 72 Secondary: % with ALT normalisation % with HBsAg loss % with HBsAg seroconversion	Not stated

	fax to the investigators after computer generated randomisation by the central monitor Sample size calculation given: 27 patients per group required to provide 80% power at p=0.05 to detect a difference in response rates of 30% between arms; increased to 30 to allow for 15% drop out rate ITT analysis		cells/mm^3, history of severe psychiatric disease, substance abuse (including alcohol) or dependence, methadone maintenance, severe comorbidity and any antiviral treatment for CHB in the 3 months preceding study enrolment. Baseline characteristics Peg-IFN-a2a plus adefovir (n=30): Mean age (SD) 48.3 (10.7); Male, n (%) 22 (73); Median BMI, kg/m2 (range) 24.1 (20.6-35.7); Median ALT level, x ULN (range) 3.4 (0.8-10.6); Previous treatment IFN, n (%) 3 (10); Nucleos(t)ide, n (%) 7 (23); Median HBV DNA, log10 IU/mL (range) 5.87 (3.8-8.1); Mean histological Ishak score Grading (SD) 5.2 (3.4) Staging (SD) 2.2 (1.2) Peg-IFN-a2a (n=30): Mean age (SD) 45.9 (10.2); Male, n (%) 18 (60); Median BMI, kg/m2 (range) 25.15 (16.3-34.2); Median ALT level, x ULN (range) 1.75 (0.6-1.4); Previous treatment IFN, n (%) 2 (6.7); Nucleos(t)ide, n (%) 4 (13.3); Median HBV DNA, log10 IU/mL (range) 5.4 (4.6-7.8); Mean histological Ishak score Grading (SD) 5.8 (3.4) Staging (SD) 2.6 (1.4)	received at least one dose of study drug were included in the analysis			Adverse events	

Effect size (ITT analysis was conducted)

End of treatment at 48 weeks	Peg-IFN-a2a plus adefovir (n=30)	Peg-IFN-a2a (n=30)	Comparison
% with undetectable HBV DNA (<40IU/mL), n (%)	20/30 (66.7)	11/30 (36.7)	p=0.02
% with ALT normalisation	17/30 (56.7)	10/30 (33.3)	p=0.037
% withdrawn due to adverse events	4/30 (13.3)	4/30 (13.3)	

24 weeks follow up	Peg-IFN-a2a plus adefovir (n=30)	Peg-IFN-a2a (n=30)	Comparison
% with undetectable HBV DNA (<40IU/mL), n (%)	3/30 (10)	1/30 (3.3)	p=0.3
% with ALT normalisation	10/30 (33.3)	10/30 (33.3)	
HBsAg loss, n (%)	1/30 (3.3)	0/30 (0)	
HBsAg seroconversion, n (%)	0/30 (0)	0/30 (0)	

Authors' conclusion: In HBeAg negative CHB, combination peg IFN alpha2a plus ADV for 48 weeks is safe and resulted in greater on-treatment efficacy than peg-IFN alpha 2a monotherapy. No difference in sustained virological and biochemical response rates were observed between the two treatment regimens.

Peg IFN a + Lamivudine vs peg IFN a only or lamivudine only

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

<table>
<tr>
<td>Marcellin 2004</td>
<td>RCT

Multi centre at 54 sites in 13 countries.

Randomisation was centralised and stratified according to geographic region and ALT levels.

Blinded for peginterferon + placebo or lamivudine

Sample size calculation reported: 160 patients per group</td>
<td>N=537</td>
<td>Patients with HBeAg-negative chronic hepatitis B.

Inclusion:
Adult patients were eligible if they had been negative for HBeAg and positive for anti-HBe antibody and HBsAg for at least six months, had an HBV DNA level of > 100,000 copies per millilitre, had a serum ALT that was greater than 1 but less than 1 but less than or equal to 10 x ULN, and had had findings on a liver biopsy within previous 24 months consistent with the presence of chronic hepatitis B, with evidence of prominent necroinflammatory activity.

Exclusion: decompensated liver disease, a coexisting serious medical or psychiatrist illness, a neutrophil count of <1500 per cubic millimetre, a platelet count of < 90,000 per cubic millimetre, a serum creatinine level that was > 1.5 times the upper limit of the normal range, a history of alcohol or drug abuse within one year before entry, treatment for chronic hepatitis B within the previous 6 months, and co-infection with HCV/HDV or HIV.

Baseline characteristics
<table>
<tr><td></td><td>PegIFNa2a + LAM (n=179)</td><td>PegIFNa2a +placebo (n=177)</td><td>LAM (n=181)</td></tr>
<tr><td>Male sex- no (%)</td><td>147 (82)</td><td>151 (85)</td><td>156 (86)</td></tr>
<tr><td>Age (yr) (Mean</td><td>41±10.8</td><td>40±11.7</td><td>40±11.1</td></tr>
</table>
</td>
<td>Group 1
180µg of pegIFNa2a once weekly +oral 100mg lamivudine once daily for 48 weeks(n=179)

Loss to follow up/reason: 7

17 either did not complete treatment or did not complete follow-up.

Overall 6 did not receive study medication, and all nine patients from a single centre were excluded owing to irregularities in study</td>
<td>Group 2
180µg of pegIFNa2a once weekly +oral placebo once daily for 48 weeks. (n=177)

Loss to follow up/reason: 5

12 either did not complete treatment or did not complete follow-up.

Group 3
100 mg lamivudine once daily for 48 weeks (n=181)

Loss to follow up/reason: 3

26 either did not complete treatment or did not complete</td>
<td>48 weeks treatment + 24 weeks follow up</td>
<td>Primary: Suppression of HBV DNA levels to below 20,000 copies per millilitre; Normalisation of ALT

Secondary: HBsAg loss; HBsAg seroconversion Mean reduction in HBV DNA; Histologic response [defined as a reduction of at least two points in the modified Histologic Activity Index score as compared with the pre-treatment score; Suppression of HBV DNA to below 400 copies per millilitre</td>
<td>Roche</td>
</tr>
</table>

	required for power of 80% to detect a difference in response rate of 15% (p=0.025); increased to 175 to allow for withdrawals		±SD)				conduct.	follow-up.		
			Alanine aminotransferase-IU/litre (Mean ±SD)	90.8±76.2	94.4±85.9	105.7±128.2				Incidence of resistance (YMDD mutation) Adverse events
			HBV DNA – log copies/ml (Mean ±SD)	7.35±2.00	7.14±1.84	7.24±1.78				
			Bridging fibrosis or cirrhosis-no (%)	40 (22)	54 (31)	53 (29)				
			Prior use of lamivudine - no (%)	15 (8)	7 (4)	9 (5)				
			Prior use of interferon alfa- no (%)	18 (10)	11(6)	14 (8)				
			White Asian Black Other	65 (36) 111 (62) 2 (1) 1 (1)	66 (37) 107 (60) 3 (2) 1 (1) #	69 (38) 111 (61) 0 1 (1)				

Effect size

Outcomes	PegIFNa2a +lamivudine (n=179)	PegIFNa2a +placebo (n=177)	Lamivudine (n=181)

End of treatment (week 48)			
Normalisation of ALT – no. (%)	87 (49)	67 (38)	132 (73)
HBV DNA < 20,000 copies/ml- no (%)	164 (92)	144 (81)	154 (85)
HBV DNA <400 copies/mL	156/179	112/177	133/181
Change in HBV DNA - mean log copies/ml -95% CI –log copies/ml	 -5.0 -4.7 to -5.3 n=165	 -4.1 -3.8 to -4.5 n=166	 -4.2 -3.9 to -4.5 n=174
24 weeks follow up			
Normalisation of ALT – n	107/172	105/172	80/178
HBV DNA < 20,000 copies/ml- n	79/172	76/172	53/178
HBV DNA <400 copies/mL n	35/172	34/172	12/178
Change in HBV DNA - mean log copies/ml -95% CI –log copies/ml	 -2.4 -1.9 to -2.8 n=170	 -2.3 -1.9 to -2.7 n=165	 -1.6 -1.2 to -2.0 n=154
Histologic response- improved- no (%) of those with paired biopsy samples	68/143	85/143	72/125
Necroinflammatory activity –improved- no (%)	66/143	79/143	57/125
Fibrosis – improved – no (%)	18/143	21/143	22/125
HBsAg loss	5/172	7/172	0/178
HBsAg seroconversion	3/172	5/172	0/178
YMDD mutation	1/173	32/179	not stated
Discontinuation for safety reasons	7/177	13/177	0/181
Death	0	(1)*	0

*thrombotic thrombocytopenic purpura developed in this patient.

Authors' conclusion: Patients with HBe-Ag negative chronic hepatitis B had significantly higher rates of response, sustained for 24 weeks after the cessation of therapy,

with peginterferon alfa-2a than with lamivudine. The addition of lamivudine to peginterferon alfa-2a did not improve post-therapy response rates.

E.6.2 Pharmacological monotherapies and combination treatments in children

E.6.2.1 Adefovir vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jonas et al. 2008	RCT- double blinded Multicentre: Setting: 12 sites in the USA and 14 sites in Europe Central randomisation. Randomisation: stratified by age (2 to <7y; >7 to <12y; >12 to <18y) and prior	N= 173	Patients with Chronic hepatitis in children aged 2 to 17 years. Inclusion: HBsAg present for at least 6 months prior to randomisation (HBsAg must have been positive at the initial screening visit that is within 4 weeks of the first dose), HBeAg (+) at screening, serum HBV DNA ≥1x10^5 copies by a PCR assay at either the initial or confirmatory screening visits, serum ALT ≥1.5 x ULN at both initial screening and confirmatory screening visit, and compensated liver disease. They were also required to have adequate renal function, hematologic function, negative serologic tests for HIV, hepatitis D, and hepatitis C, and alfa fetoprotein levels less than 50 ng/ml. Exclusion: Subjects were excluded if they had received any treatment for chronic hepatitis B within 6 months of enrollment, had evidence for other liver diseases, had received bone marrow or organ transplants or had	Adefovir (age 2 to <7 years: 0.3mg/kg once daily; age ≥7 to <12 years: 0.25mg/kg once daily; age ≥12 to <18 years: 10 mg once daily) (n=118) Total duration of treatment: minimum 48 weeks	Placebo (n=58) Total duration of treatment: minimum 48 weeks Loss to follow up: n=0; discontinued n=0	No follow up	Primary: HBV DNA <1000 copies/mL and normal ALT at week 48 Secondary: change from baseline HBV DNA; change in ALT; proportion of subjects with HBV DNA < 1000 copies/mL by study visit; proportion at week 48 with HBV DNA <lower limit of quantitation (LLQ, i.e. 29 IU/mL or 169	Gilead Sciences

	treatment. No details of allocation concealment.		received immunosuppressive, nephrotoxic, or hepatotoxic medications within 2 months of enrollment. Baseline characteristics (Adefovir (n=115) / Placebo (n=58)) Mean age (SD): 10.8 (4.3) / 10.7 (3.9) Male (%): 74 (64) / 39 (67) Mean (SD) HBV DNA log_{10} copies/ml: 8.74 (0.894) / 8.67 (1.016) ALT mean (SD), U/L: 111 (81.6) / 99 (52.8) HBeAg (+) (%): 113 (98) / 57 (98) Race (%) White: 70 (61) / 41 (71) Asian: 29 (25) / 12 (21) Black or African American: 11 (10) / 3 (5) 1(<1) / 0 Other: 4(4) / 2 (3) Prior CHB treatment: 64 (56%) / 33 (57%) No significant difference between the groups for any baseline characteristics.	Loss to follow up: n=0 ; discontinued n=3 [adverse event n=1; non compliance n=2]			copies/mL), <400, <1000, <10,000 and ≥10,000 copies/mL; normal ALT by study visit; HBeAg loss; HBeAg seroconversion; proportion of subjects with HBeAg + at baseline with HBV DNA <1000 copies/mL, normal ALT and HBeAg seroconversion; HBsAg loss; adverse events	

Effect size

Outcomes (week 48)	Adefovir (n=115)	Placebo (n=58)	p value
Mean log_{10} reduction of HBV DNA from baseline	Shown graphically only	Shown graphically only	Not reported
% with continuing undetectable HBV DNA (<169 copies/ml or 2.23log10 copies/mL) (SD)	13 (11%)3 (13%)6 (17%)4 (7%)	1 (2%)1 (8%)00	

Total 2-6 years 7-11 years 12-17 years			Not reported
Incidence of ADV resistance	No subject developed rtA181V or N236T mutation associated with ADV resistance by week 48. The rtA181T mutation was identified in 3 lamivudine-experienced subjects at baseline and week 48 in the ADV group	No subject developed rtA181V or N236T mutation associated with ADV resistance by week 48.	Not reported
Primary endpoint: Serum HBV DNA <1000 copies/ml and normal ALT Total 2 -6 years 7-11 years 12-17 years	 22/115 (19.1%) 13% (n=3) 17% (n=6) 23%	 1/58 (1.7%) 8% (n=1) 0 0%	 <0.001 Not significant Not significant 0.007
% with ALT normalisation Total 2 -6 years 7-11 years 12-17 years	 56% 30% 58% 64%	 21% 25% 16% 22%	 <0.001 Not significant 0.004 <0.001
% with HBeAg loss	Not reported	Not reported	Not reported
HBeAg seroconversion	18/113 (15.9%)	3/57 (5.3%) (all adolescents)	0.051
HBeAg seroconversion plus serum HBV DNA < 1000 copies/mL plus normal ALT, HBeAg seroconversion or HBeAg loss	Not reported	Not reported	Reported as not significant in any age group
% with HBsAg seroconversion	1	0	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported
Treatment-related adverse events Asymptomatic elevations in serum creatine kinase	14% 21.7%	10% 25.9%	Not reported

Grade 4 elevations in serum creatine kinase	2 (1.7%)	1 (1.7%)	
Increase in ALT meeting definition of severe hepatic flare	3	0	Not reported
% withdrawn due to adverse events	1 (judged unrelated to study treatment)	0	--
Death	0	0	

Safety:

The same percentage of subjects in the adefovir and placebo groups reported adverse events (83%) most of which were mild or moderate (Grade 1 or 2) and judged by the investigator to be unrelated to treatment. The most common adverse events in both treatment groups were typical childhood illnesses and their signs and symptoms. There were no adverse effects on renal function. No subject experienced hepatic decompensation.

Treatment related adverse events were reported for 14% of adefovir treated and 10% placebo treated subjects.

No study subject died. A total of 6% of adefovir treated and 9% of placebo treated subjects had at least one serious adverse event. The only treatment related serious adverse event in an adefovir subject was a Grade 3 increase in hepatic enzymes that resolved during continuing study treatment.

Overall, adefovir treatment was well tolerated in all age groups in this study in paediatric subjects with chronic hepatitis B.

Note:

There were no statistically significant differences in either the primary outcome response of HBeAg seroconversion by sex, race/ethnicitiy or genotype.

Sample size calculation:

The sample size was determined such that the study could detect a 20% difference between treatment arms across all age groups, assuming 80% power using a two sided Fisher's exact test with alpha set at 0.05.

Authors' conclusion:

Adefovir showed significant antiviral efficacy in subjects aged 12 to 17 years with HBeAg+ chronic hepatitis, but was not different from placebo in subjects aged 2 to 11 years.

Follow up study: Jonas 2012

After the 48 weeks of randomised treatment, all placebo-treated subjects who did not exhibit HBeAg seroconversion at week 44 , and all adefovir treated subjects, were offered open label ADV for up to 192 additional weeks. Treatment was discontinued if there was no virological effect, except for adolescents with previous lamivudine exposure, in who lamivudine was added to ADV. Of the 170 subjects who completed the 48-week RCT, 162 participated in the open label study. ADV was discontinued in 61 subjects due to virologic failure. In subjects who continued, continued viral suppression and ALT normalisation were noted. HBeAG seroconversions were noted in 55 subjects; HBsAg seroconversion in 5. Resistance to ADV was noted in 1 child on ADV monotherapy.

E.6.2.2 Lamivudine vs placebo

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jonas 2002	RCT- double blinded Multi centre (40 centres in North America, South America and Europe) Randomisation was performed at a central location. Allocation concealment not reported.	N=288	Children with chronic hepatitis B. Inclusion: Eligibility requirements included age between 2 and 17 years at enrollment, seropositivity for hepatitis B surface antigen (HBsAg) for at least 6 months before enrollment, seropositivity for HBeAg, undetectable levels of antibody against HBeAg (anti-HBeAg), serum alanine aminotransferase values that were more than 1.3 times the upper limit of the normal range (but less than 500 IU per litre) for at least 3 months before enrollment, evidence of inflammation on liver biopsy, and measurable HBV DNA in serum on branched chain DNA assay. Exclusion: Patients were excluded if they had received interferon within the previous 12 months or systemic antiviral agents, immunomodulatory drugs, cytotoxic agents or corticosteroids within the previous 6 months. Patients were also excluded if they were co-infected with HIV, or hepatitis C virus, or hepatitis D virus, or if they had decompensated liver disease, renal insufficiency, pancreatitis, a clinically significant co-existing medical illness or other types of liver disease. Women who	Lamivudine (n=191) Lamivudine 3mg/kg body weight (maximum dose, 100 mg) once daily Total duration of treatment: 52 weeks Loss to follow-up: lamivudine group= 6 withdrew from the study (2 lost to follow-up,	Placebo (n=97) Matching placebo solution orally once daily Total duration of treatment: 52 weeks Loss to follow-up: placebo group= 1 did not receive placebo (withdrew consent	No follow up	Primary: virologic response (absence of serum HBeAg and serum HBV DNA) at 52 weeks Secondary: Sustained normalisation of the alanine aminotransferase values; seroconversion from HBeAg to anti-HBe; loss of HBsAg; loss of HBeAg; The absence of detectable levels of HBV DNA in serum. Incidence of	Glaxo-Smith Kline

			were pregnant or breast feeding were excluded. Liver biopsy to determine eligibility had to have been performed within 24 months before enrollment and at least 12 months after the completion of interferon therapy (for patients who had received interferon). Baseline characteristics			2 withdrew consent, 1 had adverse event, 1 was non-compliant with therapy)	before first dose), 4 withdrew from the study (2 lost to follow-up, 1 withdrew consent, 1 had adverse event)		resistance	

Characteristic	Lamivudine group (n=191)	Placebo group (n=96)
Age yr- mean	9	8
Weight Median — kg Range — kg	 32 13–94	 30 11–80
Sex- no (%) male	123 (64)	61 (64)
Racial or ethnic origin — no. (%) White Asian Black Hispanic Other	 139 (73) 33 (17) 11 (6) 4 (2) 4 (2)	 60 (63) 22 (23) 9 (9) 2 (2) 2 (2)
HBV DNA — meq/ml Median Range	 895 2.2–28,300	 1032 1.7–15,010
Alanine aminotransferase — no. of times the upper limit of the normal range Median (Range)	This should be median 2.1	This should be median 2.3 2.1 (0.7–

Mean	2.3 (0.3–22.1) 3.2	16.9) 2.7
No response to prior interferon treatment — no. (%)	40 (42) This should be 47%	89 (47) This should be 42%

There were no significant differences in demographic characteristics between the treatment groups.

Effect size

Outcomes at week 52	Lamivudine group (n=191)	Placebo group (n=95)	Odds ratio (OR; 95% CI)	p-value
Virologic response (absence of serum HBeAg and serum HBV DNA) at 52 weeks n (%)	44/191 (23%)	12/95 (13%)	2.1 (1.0 to 4.1)	0.04
Sustained normalisation of alanine aminotransferase level** n(%)	100/191 (55%)	11/95 (12%)	8.4 (4.2 to 16.9)	<0.001
Virologic response and acquisition of anti-HBe n(%)	42/191 (22%)	12/95 (13%)	1.9 (1.0 to 3.9)	0.06
Incidence of resistance	31/166	0/86	Not reported	Not reported
Loss of HBeAg n (%)	50 /191 (26%)	14/95 (15%)	2.1 (1.1 to 3.9)	0.03
HBV DNA undetectable*** n(%)	117/191 (61%)	15/95 (16%)	8.4(4.5 to 15.7)	<0.001
Loss of HBsAg n(%)	3/191 (2%)	0	-	-
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported	Not reported

**only patients with baseline alanine aminotransferase levels that exceeded the upper limit of the normal range were included in the analysis (88 in the placebo group and 183 in the lamivudine group)

***levels were undetectable on branched chain DNA assay with a lower limit of detection of 0.7 meq per millilitre.

Adverse events:

The nature, incidence and severity of adverse events in patients receiving lamivudine were similar to those in patients receiving placebo. There were no deaths during the study.

Authors' conclusion:
In children with chronic hepatitis B, 52 weeks of treatment with lamivudine was associated with a significantly higher rate of virologic response than was placebo.

Data from this study were analysed (Hom 2004) to identify pre-treatment factors that predicted the likelihood of virologic response. In univariate analyses, treatment with lamivudine (p=0.039), higher baseline ALT (p<0.001), higher histologic activity index (HAI, p<0.001) and lower HBV DNA level (p=0.038) predicted greater response, but in multivariate analyses, only baseline ALT (OR 1.08, 95% CI 1.04 to 1.12, p<0.001 for every 10 units/mL increase) and HAI score (OR 1.18, 95% CI 1.03 to 1.35, p=0.019) were predictive in addition to treatment with lamivudine versus placebo (OR 3.89 (95% CI 1.66 to 9.08, p=0.002).

Follow up studies including participants from this trial have been published (Sokal 2006, Jonas 2008A) but some subjects had additional treatments after the randomised therapy so the outcomes cannot be included in this review.

E.6.2.3 IFN α2b vs no therapy

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sokal 1998	RCT-unblinded Multinational (18 centres from Belgium, France, Canada, and the United	N=149	HBeAg (+) Inclusion: Inclusion criteria were: age between 1 and 17 years; known presence of hepatitis B surface antigen in serum for at least 6 months; presence of HBV DNA and hepatitis B e antigen in serum on	IFN-α 2b (n=72) Dose: IFN-α 2b starting at 3 megaunits/m^2 of body surface area 3 times a week	no therapy (n=77) Control group patients were monitored at less regular intervals on no therapy.	24 weeks treatment + 24 weeks follow-up after end of treatment	Primary: persistent loss of HBV DNA and HBeAg 24 weeks after end of treatment (i.e. 48 weeks after enrolment). Secondary: Loss of HBsAg	Not reported Schering Plough staff are thanked in the acknowledgements

	States) Randomisation was done centrally. Randomisation was stratified by patient age (1-12 vs. 13-17 yrs) and by whether the patient was of Asian ethnicity. Allocation concealment not reported.		two or more determinations at least 1 month apart during the pr-enrollment monitoring period; elevations in serum alanine aminotransferase activities on four determinations taken at least 1 month apart during the previous 6 months with no values below 1.5 times the upper limit of the normal range and the average value equal to or above 2 times the upper limit of the normal range; histological evidence of chronic hepatitis on liver biopsy taken within 18 months before enrollment; normal haematocrit (>34%); white blood cell count (>4000/mm3); platelet count (>150,000/mm^3); normal serum albumin levels (>3.5 g%); normal serum creatinine (<1 mg/dl); negative serum pregnancy test result. Exclusion: Previous therapy with IFN-α; concurrent participation in another clinical trial; therapy with corticosteroids or antiviral agents in the previous 12 months; hepatic decompensation as marked by a history of ascites, variceal haemorrhage, or hepatic encephalopathy; epilepsy or serious central nervous system disease; psychiatric illness; presence of antibody to hepatitis C virus or	for 1 week; dose increased to 6 mega units/m^2 of body surface area at second week, and continued for a minimum of 16 weeks and a maximum of 24 weeks based on results of virological testing for evidence of response. Treatment was stopped at 16 or 20 weeks if HBeAg was undetectable on 2 serum determinations taken 1 month apart. Total duration of treatment: 16-24 weeks Loss to follow up/reasons: 2/72 children in the	After 48 weeks of observation, untreated patients who continued to meet the entry criteria were eligible to receive IFN-α 2b according to the same regimen on a compassionate use basis. Total duration of treatment: 16-24 weeks Loss to follow up/reasons: 3 of the untreated control patients were not included: 1 was HBV DNA negative at entry, 1 had ALT levels below the entry criteria at entry, and 1 did not return for		ALT normalisation Improvements in serum aminotransferase concentrations HAI in a subset of 10 patients (treated group only) Adverse events	

			hepatitis D virus; presence of another cause of liver disease; presence of antibody to HIV; pregnancy, breast feeding, or inability to practice birth control during the study. Baseline characteristics IFN-α (n=72) / Control (n=77) Median age (range): 5 (1-17) / 5 (1-17) Median weight (range), kg: 18.5 (10-64) / 19 (10-83) Sex (% male): 42 (58) / 48 (62) Median serum HBV DNA (range), (pg/ml): 88.1 (<0.7-699) / 80 (<0.7-705) Median serum ALT (range), times ULN: 3.2 (1.7-18.3) / 3.7 (1.3-18.2) Race (%) White: 37 (51) / 39 (51) Black: 12 (17) / 9 (12) Asian: 9 (13) / 11 (14) Other: 14 (19) / 18 (23)	treatment group were not treated because they had become HBV DNA negative immediately before scheduled to start therapy. Follow-up completed in 70 children.	observation.				

			There were no significant differences between the treatment and control groups in any baseline characteristic.					

Effect size

	IIFN-α 2b (n= 70)	Control (no therapy) (n=74)	p value
Log reduction of HBV DNA	Not reported	Not reported	--
Undetectable HBV DNA at week 24 (end of treatment) Undetectable HBV DNA at week 48 (24 weeks after end of treatment)	18/70 (26%) 23/70 (32.9%)	8/74 (11%) 8/74 (11%)	p=0.029 Not reported
Incidence of resistance	Not reported	Not reported	Not reported
% with ALT normalisation at week 48 (24 weeks after end of treatment)	12/70	13/74	Not reported
Lost HBeAG at week 48 (24 weeks after end of treatment)	23/70 (32.9%)	8/74 (11%)	Not reported
HBsAg loss and/or seroconversion n (%)	7 (10%)	1(1.2%)	0.03
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported
Any adverse events n (%)	70 (100)	25 (35)	<0.01
% withdrawn due to adverse events	Not reported separately for groups		Not reported

Withdrawals due to adverse events:

Therapy was discontinued early in 3 (4%) children, the reasons being anorexia (9 weeks), fever and chills (4 weeks), and -neutropenia (19 weeks) [Not reported separately for groups]. 12 children required hospitalisation during the 1 year after enrollment, but for reasons not clearly related to treatment. Among treated patients, hospitalisations (n=5) were for bone fracture, musculoskeletal pains, respiratory syncytial virus infection, appendicitis, and abdominal trauma. In the control group, hospitalisations (n=7) were required for asthma, pneumonia, adenoidectomy, surgery for strabismus, otitis media, and an undiagnosed febrile illness with vomiting.

Authors' conclusion:

In children with chronic hepatitis B, INF-α promotes loss of viral replication markers and surface antigen and improves aminotransferases and histology.

Notes:

Correlation of response with baseline characteristics:

The response rate to therapy was comparable between Asian and non-Asian patients (22% vs. 26%). The response rate tended to be higher in younger children (27% in children <13 years vs. 14% in those >13 years) and higher in girls (41%) than in boys (15%). Treated patients with baseline HBV DNA levels <50 pg/ml had twice the response rate (41%) as those with levels between 50 and 200 pg/ml (23%) and almost 6 times that of patients with levels >200 pg/ml (7%). There was no difference in response rates of treated patients by differences in ALT levels or HAI scores.

E.6.2.1 IFN α2a + lamivudine vs IFN α2b + lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ozgenc 2004	RCT-unblinded No details of randomisation and allocation concealment. Turkey	N=63	Children with chronic hepatitis B- HBeAg (+) Inclusion: Inclusion criteria were presence of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), absence of hepatitis surface and e antibody (anti-HBs, anti-HBe), and presence of HBV DNA in serum screened at 3 month intervals for at least 1 year, serum ALT levels more than 1.5 times the upper normal limit (40IU/L), and histological evidence of chronic hepatitis with histological activity Index (HAI) more than 6 by liver biopsy. Exclusion: Patients with accompanying hepatitis D, C or HIV infection, and underlying autoimmunity or chronic illness were excluded from the study. Platelets counts less than 150,000/mm3 and white cell counts less than 5000/mm3 were other exclusion criteria. Baseline characteristics {table1}	IFN-α2a (5MU/m2 thrice weekly + lamivudine (4mg/kg/day, max 100 mg/day) (3TC) (n=29) Total duration of treatment: 6 months combination then 6 months lamivudine alone Loss to follow up/reasons: all patients completed the study at 12 months	IFN-α2b (5MU/m2 thrice weekly) + lamivudine (4mg/kg/day, max 100 mg/day) (3TC) (n=34) Total duration of treatment: 6 months combination then 6 months lamivudine alone Loss to follow up/reasons: all patients completed the study at 12 months	End of therapy (12 months) plus 12 months after end of treatment (24 months in all)	% with undetectable HBV DNA Serum ALT and % with ALT normalisation HBeAg clearance and anti-HBe seroconversion Anti-HBs seroconversion Response rate (HBV DNA clearance + HBeAg/anti-HBe seroconversion and ALT normalization at the end of therapy) Breakthrough (re-emergence of HBV DNA	Not reported

{table1}

	IFN-α2a +lamivudine (3TC) n=29	IFN-α2b+lamivudine (3TC) n=34.	p-
Mean age (yrs)	11.1±3.8	9.5±3.3	0.07
Sex (male/ female)	9/20	9/25	0.78

			HBV DNA positivity (%)	100	100				in serum after clearance (but authors did not study mutation)	
			Mean (SD) serum ALT U/L	96.6±49.2	91.6±30	0.79				
			HBsAg positivity (%)	100	100					
			HBeAg positivity (%)	100	100					
			Anti-HBe (%)	-	-					
			Mean (SD) HAI	7.1 (2.1)	7.3 (2.2)	0.55				
			The two treatment groups had similar baseline clinical and virological characteristics							

Effect size

Post-treatment (end of treatment - 12 months)	IFN-α2a +lamivudine (3TC) (n=29)	IFN-α2b+lamivudine (3TC).(n=34)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
% with undetectable HBV DNA	26/29 (89.7%)	33/34 (97.1%)	0.32
Incidence of resistance	Not reported	Not reported	Not reported
Breakthrough incidence - n (%)	1 (3.4)	0	0.46
Serum ALT levels IU/L	30.1 (21.1)	33 (11.8)	0.06
% with ALT normalisation - n (%)	24 (82.8%)	32 (94.1%)	0.23
HBeAg clearance month 12	14/29 (48.3%)	17/34 (50%)	1.0
HBeAg clearance month 18	13/29 (44.8%)	16/34 (47.1%)	1.0

HBeAg seroconversion - n (%)	15 (42.9)	16 (45.7)	1.0
HbsAg seroconversion - n (%)	3 (10.3)	0	0.09
Response rate (HBV DNA clearance + HBeAg/anti-HBe seroconversion and ALT normalization at the end of therapy)	13/29 (44.8%)	16/34 (47.1%)	1.0
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported
% withdrawn due to adverse events	Not reported		

Adverse events:

Malaise, fatigue and fever were seen in 100% of children during IFN treatment. Leukopenia and thrombocytopenia was detected in one patient (3.4%) receiving IFN-α 2a and 2 patients (5.8%) receiving IFN-α 2b, which responded to dose reduction (3 MU/m2) (p=0.47).

Authors' conclusion:

No significant difference was found in response rates achieved by combination therapies based on IFN-α2a and IFN-α2b. Clinical efficacy of lamivudine and two different IFN subtypes was found similar.

E.6.2.2

Interferon α 2b plus lamivudine (6 months) versus Interferon α 2b plus lamivudine (12 months)

Reference	Study type	Number of patients	Patient characteristics	Comparison	Intervention	Length of follow-up	Outcome measures	Source of funding
Dikici 2001	RCT No details of randomisation	N=57	Children with chronic hepatitis B infection Inclusion: hepatitis B surface antigen (HBsAg) for at least 6 months, hepatitis HBeAg, absence of	Group 1: interferon α 2b 10 million units (MU)/m^2 3 days a week	Group 1: interferon α 2b 10 million units (MU)/m^2 3	6 months after end of therapy	Complete response: HBeAg/Anti-HBe seroconversion, clearance of	not stated

	or allocation concealment Not blinded (open trial) Turkey		hepatitis B surface antibody and hepatitis B e antibody (anti-HBe), ALT levels greater than 1.5 times ULN (40 IU/L), HBV DNA and histological evidence of chronic heptatitis on liver biopsy taken within 6 months before enrolment. Exclusion: age younger than 2 years, presence of hepatitis delta and C virus antibodies, no other immunocompromising drugs, platelet count <150,000/mm^3, leucocyte counts <3000/mm^3, haemoglobin <10g/dL, epilepsy or serious central nervous system disease, psychiatric disease, kidney insufficiency and hepatic decompensation. Baseline characteristics	by sc injection plus lamivudine 4mg/kg/day (maximum 100mg) for 6 months Total duration of therapy 6 months	days a week by sc injection plus lamivudine 4mg/kg/day (maximum 100mg) for 12 months Total duration of therapy 12 months		HBV DNA and normalization of ALT. Lack of one of these = partial response; lack of 2 considered non-response	

Characteristic	Group 1 (6 months) n=30	Group 2 (12 months) n=27
Mean (SD) age	7.7 (2.8)	8.5 (3.2)
Sex (% male)	63	67
HBV DNA <100pg/mL (n)	1	0
HBV DNA >2000pg/mL (n)	24/30	25/27
Mean (SD) serum ALT, U/L	99 (58)	121 (66)
ALT > 100 IU/L (n)	17	14

Mean HAI	6.7	8.1

Effect size

	Group 1 (6 months) n=30	Group 2 (12 months) n=27	p value
ALT at end of therapy IU/L	43.6 (27.2)	27.8 (11.5)	not reported
ALT normalization at end of therapy	18/30 (60%) (at 6 months)	21/27 (78%) (at 12 months)	not reported
HBeAg clearance at end of therapy	10/30 (33%)	16/27 (59%)	NS
HBe seroconversion at end of therapy	5/30 (17%)	10/27 (37%)	NS
HBsAg clearance at end of therapy	1/30 (3%)	5/27 (18.5%)	NS
HBs seroconversion at end of therapy	2/30 (7%)	2/27 (7%)	NS
Undetectable HBV DNA	29/30 (97%)	27/27 (100%)	NS
Complete response: HBeAg/Anti-HBe seroconversion, clearance of HBV DNA and normalization of ALT	5/30 (17%)	10/27 (37%)	NS

	Group 1 (6 months) n=30	Group 2 (12 months) n=27	p value
ALT normalization 6 months after end of therapy	23/30 (70%) (at 12 months)	23/27 (85%) (at 18 months)	not reported
HBeAg clearance 6 months after end of therapy	11/30 (37%)	15/27 (56%)	NS
HBe seroconversion 6 months after end of therapy	6/30 (20%)	10/27 (37%)	NS
HBsAg clearance 6 months after end of therapy	2/30 (7%)	5/27 (18.5%)	NS
HBs seroconversion 6 months after end of therapy	2/30 (7%)	2/27 (7%)	NS
Undetectable HBV DNA	29/30 (97%)	26/27 (96%)	NS
Complete response: HBeAg/Anti-HBe seroconversion, clearance of HBV DNA and normalization of ALT	6/30 (20%)	10/27 (37%)	NS

Adverse events: Patients tolerated the treatment well. Therapy was not discontinued because of flu-like syndrome and gastrointestinal symptoms, which are the most common side effects. Hair loss from combined therapy which occurred in 8 cases in group 1 and 7 cases in group 2 usually began after 2 to 3 months of treatment and continued for several months after treatment was stopped. No child developed severe neutropenia, thrombocytopenia or any other complication of bone marrow

suppression.

Authors' conclusion: When the combination of Interferon alpha 2 b plus lamivudine in children was compared at teh end of therapy and 6 months after therapy, normalization of ALT and the clearance of HBeAg and HBsAg in both groups were directly proportional to the duration of treatment. However, the higher complete response rate at 12 months of combination therapy was not statistically significantly different from that at 6 months.

E.6.3 Sequential therapies

E.6.3.1 HBeAg negative antiviral naïve patients with CHB

Switching from lamivudine alone to combination treatment of lamivudine plus interferon alpha-2b versus continuing lamivudine

Reference	Study type	Number of patients	Patient characteristics	Comparison	Intervention	Length of follow-up	Outcome measures	Source of funding
Shi 2006	RCT No details of randomisation	N= 162	Chinese patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (patients previously untreated with antiviral agents). Inclusion: Patients over 16 years of age, positive for hepatitis B surface antigen (HBsAg) for at least 6 months,	Group A (sequential treatment); lamivudine alone (100 mg per day) for 20	Group B; Lamivudine alone (100mg per day) (n=98)	48 weeks of treatment plus 24 weeks follow up	normalization of ALT levels undetectable HBV DNA (<1000 copies/mL)	Grants from the National Natural

	Allocation concealment unclear Blinding not reported.		negative for HBeAg and positive for hepatitis B e antibody (anti-HBe), and had HBV DNA levels of more than 100 000 copies/mL and serum ALT levels greater than 1.5 times but less than 10 times the normal range according to recommendations of Chinese Experts Committee for Clinical Use of Lamivudine. Exclusion: co-infection with hepatitis A, C, D and E virus or HIV, decompensated liver diseases or HCC, a history of alcohol or drug abuse within 1 year before entry, other possible causes of chronic liver damage, and previous treatment of chronic hepatitis B. Baseline characteristics Characteristic / Group A (n=64) (Sequential treatment) / Group B (n=98) (lamivudine alone) / p-value Median age (range): 35 (21-56) / 32 (20-57) / NS Sex (% men): 38 (60%) / 78 (80%) / (P < 0.05) serum HBV DNA (mean±SD) (range), log10 copies/ml: 6.73 ±1.16 (5.01–9.01) / 6.85 ±0.97 (5.02–9.12) / (P > 0.05) serum ALT (mean±SD) (range), U/L: 135.59±90.81 (60–282.00) / 120.47 ±65.71 (56.00–300.00) / P > 0.05 All the patients were Chinese and well matched in terms of age, weight and laboratory results at baseline. However, the percentage of males was lower in group A	weeks followed by lamivudine + interferon-alfa-2b (5 million units three times per week) for 4 weeks followed by interferon-alfa-2b alone (5 million units three times per week) for 24 weeks.(n=64) Total duration of treatment: 48 weeks Loss to follow up/reasons: No loss to follow-up	Total duration of treatment: 48 weeks Loss to follow up /reasons: No loss to follow-up		Lamivudine resistant mutations HBsAg loss or seroconversion	Science Foundation of China and the Foundation for Distinguished Young Scholars from National Natural Science Foundation of China

			than in group B.				

Effect size

Outcomes (week-24)	Group A (Sequential treatment) (n=64)	Group B (lamivudine alone) (n=98)	p value
Undetectable HBV DNA <1000 copies/ml	52/64 (81)	76/98 (78)	>0.05
Incidence of resistance	2/64 (3.13)	6/98 (6.12)	Not reported
% with ALT normalisation	28/64 (44)	72/98 (73)	<0.05
% with HBeAg loss and/or seroconversion	Not reported	Not reported	Not reported
% with HBsAg loss and/or seroconversion	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

Outcomes (week 48)	Group A (n=64) (Sequential treatment)	Group B (n=98) (lamivudine alone)	p value
Undetectable HBV DNA <1000 copies/ml	36/64 (56)	54/98 (55)	>0.05
Incidence of resistance	0/64	22/98 (22.45)	Not reported
% with ALT normalisation	38/64 (59)	54/98 (55)	>0.05
% with HBeAg loss and/or seroconversion	Not reported	Not reported	Not reported
% with HBsAg loss and/or seroconversion	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

Outcomes (week 72, i.e. 24 weeks of follow up)	Group A (n=64) (Sequential treatment)	Group B (n=98) (lamivudine alone)	p value
Undetectable HBV DNA <1000 copies/ml	9/64 (14)	18/98 (18)	>0.05
Incidence of resistance	Not reported	Not reported	Not reported

% with ALT normalisation	34/64 (53%)	36/98 (36%)	<0.05
% with HBeAg loss and/or seroconversion	0	0	Not reported
% with HBsAg loss and/or seroconversion	0	0	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

HBsAg response:

At week 72, HBsAg loss or seroconversion was not identified in either group A or group B.

Lamivudine-resistant mutations

No patients had evidence of lamivudine-resistant mutations at baseline and YMDD mutants were monitored in all patients every 12 weeks thereafter. Only two patients (3.13%) were found with the YIDD variant at week 24 and no patients had evidence of YMDD mutations at week 48 among 64 patients in group A. The two patients who had YIDD variants at week 24 had normalized ALT and undetectable HBV DNA at week 48 and week 72. In contrast, YMDD mutations were found in six patients (four YIDD variants and two YVDD variants, 6.12%) at week 24 and in 22 patients (12 YIDD variants, eight YVDD variants and two with a mixture of YIDD and YVDD variants, 22.45%) at week 48 from group B ($P < 0.05$). All the 22 patients who had YMDD mutations at week 48 had rebounds of serum HBV DNA and 18 (82%) had rebounds of ALT levels.

Adverse events

Lamivudine was well tolerated and no adverse symptoms were identified during treatment. During the course of interferon, six patients had serious adverse events including pyrexia, fatigue, myalgia and headache. All the patients completed their treatments.

Authors' conclusion:.

Sequential treatment of chronic hepatitis B with lamivudine and interferon-alfa 2b monotherapies is as effective as lamivudine-alone treatment in Chinese patients. However, sequential treatment can significantly suppress the emergence of lamivudine-resistant mutations.

Notes:

No details of sample size calculation

E.6.3.2 HBeAg negative lamivudine resistant patients with CHB

Switching from lamivudine plus adefovir combination therapy to adefovir monotherapy verus continuing combination therapy of lamivudine plus adefovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Aizawa 2010	RCT Blinding not reported. Randomization methods not reported. Allocation concealment was performed by means of sealed, opaque, numbered envelopes. No sample size calculation	N= 29 Setting: Japan	Chronic hepatitis B (CHB) patients with lamivudine (LAM)-resistant HBV, who responded to LAM plus ADV combination therapy Inclusion: Eligible patients had virological and biochemical breakthroughs caused by lamivudine resistant mutants during Lamivudine monotherapy and did not receive any other antiviral or immunomodulatory agent against the breakthroughs; they had responded to an initial 12 months of lamivudine plus adefovir combination therapy (HBV DNA <3.7 LGE/mL Exclusion: Exclusion criteria were liver cancer or decompensated liver cirrhosis, other forms of liver disease, coexisting serious medical illness treatment with any other antiviral or immunomodulatory agent administered within the preceding 12 weeks, and hepatitis C virus antibody.	Patients were treated with combination of lamivudine (100 mg once daily) plus adefovir (10 mg once daily) for 12 months, after that they discontinued lamivudine within 12 months after allocation and were maintained on adefovir monotherapy (overlap/ switch group) (n=14) 1 excluded from study due to moving to another city.	Lamivudine (100 mg once daily), plus adefovir (10 mg once daily) combination therapy (combination group)(n=15) Total duration of treatment: 28 months Loss to follow up/reasons: n=8	Follow-up: 19.3-36.7 months (median, 28.2 months) for the combination group and 21.0-36.4 months (29.0 months) for the overlap/ switch group	Undetectable HBV DNA <3.7 LGE/ml) ALT normalisation (%) HBeAg loss HBeAg seroconversion	GlaxoSmithKline. Fund for Clinical Research from the Department of Gastroenterology and Hepatology, Kashiwa Hospital, Jikei Univers

			Baseline characteristics <table><tr><th>Characteristic</th><th>Combination group (n=15)</th><th>Overlap/ switch group (n=13)</th><th>p-value</th></tr><tr><td>Median (range) age (years)</td><td>58 (35-74)</td><td>52 (37-69)</td><td>0.28</td></tr><tr><td>Male: female</td><td>11:4</td><td>11:2</td><td>0.47</td></tr><tr><td>HBeAg positive n (%)</td><td>5 (33)</td><td>6 (46)</td><td>0.27</td></tr><tr><td>Median (range) HBV DNA (LGE/mL)</td><td>6.5 (4.9-8.8)</td><td>7.1 (5.3-8.6)</td><td>0.16</td></tr><tr><td>Median (range) ALT (IU/L)</td><td>101 (40-785)</td><td>118 (59-700)</td><td>0.42</td></tr><tr><td>Cirrhosis</td><td>5 (36)</td><td>3 (23)</td><td>0.55</td></tr><tr><td>Genotype B:C</td><td>1:14</td><td>1:12</td><td>0.47</td></tr><tr><td>Median lamivudine pre-adefovir (months)</td><td>32.3 (6.9-52.8)</td><td>28.0 (10.0-52.5)</td><td>0.48</td></tr></table>LGE = log genome equivalent Note: n=1 from the overlap/switch group was excluded from the study as he could not attend	Subdivided into 3 groups: 5 switched to monotherapy at the time of complete virological response at 12 months; 4 switched 6 months later (i.e. 18 months) and 4 switched 12 months after CVR (i.e. at 24 months) Total duration of treatment: 29 months Loss to follow up/reasons: N=7/13				ity School of Medicine.

			the hospital due to a change of residence to another city after the randomization.					

Effect size

Outcomes- 12 months	Switching from LAM +ADF to ADF monotherapy (n=13)	Combination group (n=15)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
Undetectable HBV DNA <3.7 LGE/ml (%)	13/13	15/15	Not reported
% with ALT normalisation	13/13	12/15	Not reported
HBeAg loss	3/6	1/5	Not reported
HBeAg seroconversion	0	1	Not reported
% with HBsAg seroconversion	1/6	0/5	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

Outcomes- 24 months	Switching from LAM +ADF to ADF monotherapy (n=9)	Combination group (n=10)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
undetectable HBV DNA <3.7 LGE/ml (%)	9/9	10/10	Not reported
% with ALT normalisation	9/9	8/10	Not reported
% with HBeAg loss and/or seroconversion	4/6	1/5	Not reported
% with HBsAg loss and/or seroconversion	Not reported	Not reported	Not reported
Incidence of resistance	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver	Not reported	Not reported	Not reported

disease specific)			

Outcomes- 30 months	Switching from LAM +ADF to ADF monotherapy (n=9)	Combination group (n=10)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
Undetectable HBV DNA <3.7 LGE/ml (%)	6/6	7/7	Not reported
Incidence of resistance	Not reported	Not reported	Not reported
% with ALT normalisation	6/6	7/7	Not reported
% with HBeAg loss	3/6	2/5	Not reported
% with HBeAg seroconversion	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

Safety
No adverse events were observed in any of the patients. None of the cirrhotic patients progressed to hepatic decompensation.

Authors' conclusion:.
In LAM-resistant CHB patients who achieved complete virological response (CVR) to LAM plus ADV combination therapy, CVR was maintained after overlap/switch to ADV monotherapy, suggesting that it could be a useful regimen for such patients.

Notes:

Switching from lamivudine to adefovir monotherapy versus combination treatment of lamivudine plus adefovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Akyildiz 2007	RCT	N= 54	Patients with lamivudine-resistant hepatitis B virus (HBV) infection. Hepatitis B surface antigen positive	Switching from		3 months	1) undetectable HBV DNA levels	None reporte

	Details of randomisation not reported. allocation concealment unclear. Blinding not reported. Setting: Turkey		(men and women). Inclusion: Hepatitis B virus DNA level >5 log10 copies/ml and elevated ALT 1.2 upper limit of normal. All the patients had compensated liver disease and no history of variceal bleeding, ascites, or hepatic encephalopathy. Serum albumin levels >3 g/dl, total bilirubin levels <2 mg/dl, prothrombin time <2 seconds above upper limit of normal and Child-Pugh-Turcotte score <7. Exclusion: Exclusion criteria were as follows, serum creatinine level >1.4 mg/dl or creatinine clearance <50 ml/min, co-infection with HIV or HCV, serum AFP >50 ng/ml, previous Adefovir therapy, receiving nephrotoxic or hepatotoxic drugs, coexisting other chronic liver diseases, such as metabolic liver diseases and alcoholic liver disease, pregnancy or lactation, organ transplantation, and having malignancy. Baseline characteristics Characteristic / Group 1 (n=25) / Group 2 (N=29) Median age (range) / 48.5 (20–71) / 48 (20–69) Sex male: female / 17/8 / 17/12 HBeAg positive/negative / 8/17 / 11/18 Median serum HBV DNA (range), log10 copies/ml / 7.64 / 6.54	lamivudine to adefovir 10 mg/day (Group 1) (n=25) Total duration of treatment: 3 months Loss to follow up/reasons: not reported	Adefovir 10 mg once daily and lamivudine 100 mg once daily combination (Group 2). (n=29) Total duration of treatment: 3 months Loss to follow up/reasons: not reported	treatment and 3 and 9 months follow up	by PCR (<2000 copies/ml [lower limit of detection]) 2) ALT normalisation	d

Median serum ALT (range), U/L	80.5	60
Adefovir therapy (mo) (mean ± SD (range))	9.39 ± 5.7 (3–24)	8.16 ± 6.9 24)

There was no significant difference between groups.

Effect size

Outcomes (end of 3 months treatment)	Switching from LAM to ADF (n=25)	ADF +LAM (N=29)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
Undetectable HBV DNA>2000 copies/m	6/25	6/29	Not reported
Incidence of resistance	Not reported	Not reported	Not reported
% with ALT normalisation	10/25	13/29	Not reported
% with HBeAg loss and/or seroconversion	Not reported	Not reported	Not reported
% with HBsAg loss and/or seroconversion	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

Outcomes (end of 3 months follow up)	Group 1 (n=25)	Group 2 (N=29)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
Undetectable HBV DNA>2000 copies/m	8/25	13/29	Not reported
Incidence of resistance	Not reported	Not reported	Not reported
% with ALT normalisation	13/25	20/29	Not reported

% with HBeAg loss and/or seroconversion	Not reported	Not reported	Not reported
% with HBsAg loss and/or seroconversion	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

Outcomes- (end of 9 months follow up)	Group 1 (n=25)	Group 2 (N=29)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
Undetectable HBV DNA>2000 copies/m	14/25	17/29	0.29
Incidence of resistance	Not reported	Not reported	Not reported
% with ALT normalisation	18/25	23/29	Not reported
% with HBeAg loss and/or seroconversion	Not reported	Not reported	Not reported
% with HBsAg loss and/or seroconversion	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

ALT:

Two patients (8%) had ALT flare (more than 5 times upper limit of normal (Grade 3 toxicity)) without any clinical decompensation in Group 1. Mild ALT elevation according to baseline levels were found in eight (27.6%) and four (17.4%) patients, respectively, in Group 2 and Group 1, and there was no statistically significant difference between the two groups.

Authors' conclusion:.

This study showed that it is not necessary to continue lamivudine therapy while switching to Adefovir therapy. Adefovir alone is effective in the treatment of patients with lamivudine resistant HBV infection and compensated liver disease, without significant clinical and laboratory flares.

Notes: Outcome data read from graph - unclear

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E.6.3.3 HBeAg positive treatment naïve patients with CHB

Sequential treatment of lamivudine followed by pegylated interferon alpha-2b versus sequential treatment of placebo followed by pegylated interferon alpha-2b

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sarin 2007	RCT Randomisation-computer generated Allocation concealment unclear. Setting: India ITT used	N= 63	Treatment naïve HBeAg positive patients. Inclusion: Inclusion criteria: Adult men and women 16 to 70 year old, HBsAg positive, HBeAg positive, and anti-HBe antibody negative at the time of screening and for at least the previous 6 months, quantifiable serum HBV DNA levels of >10^5 copies per millilitre, alanine aminotransferase (ALT) levels greater than 1.2 times the upper limit of normal and less than 10 times the upper limit of normal screening and for at least the previous 3 months and treatment naïve. Exclusion: Exclusion criteria: Hepatitis C,D, or HIV infection, decompensated liver disease, evidence of liver disease because of other aetiology, serum creatinine more than 1.5 times the upper limit of normal, haemoglobin less than 10g/dl, platelet count less than 70,000 /mm^3, and white count less than 3000/mm^3, serious concurrent medical illnesses (like malignancy, severe cardiopulmonary disease, uncontrolled diabetes mellitus, alcoholism), women who were pregnant or nursing, inability to give informed written	Group B-Lamivudine 100mg daily for 4 weeks, followed by peg-IFN alpha-2b (1µg/kg) given once a week subcutaneously for 24 weeks. (n=36) Total duration of treatment: 28 weeks	Group A: Placebo for 4 weeks, followed by peg-IFN alfa 2b (1µg/kg) given once a week subcutaneously for 24 weeks. (n=27) Total duration of treatment: 28 weeks Loss to follow	Weeks 4, 28 and 52 (Patients followed for 24 weeks after treatment)	Loss of HBeAg; appearance of anti-HBe; undetectable HBV DNA by hybrid capture assay (<4700 copies/ml); Normalisation of ALT (defined as ALT≤40 IU/L)	Fulford India Limited

consent.

Baseline characteristics

Characteristic	Group A (n=27)	Group B (n=34)
age (yr) mean±SD	32±11	32.5±10.5
Sex (% men)	25 (92.6)	31 (86.1)
mean±SD HBV DNA , log_{10} copies/ml	7.515±1.56	7.575±1.50
mean±SD serum ALT , IU/L	123.9±63.5	134.2± 87.1
Mean (SD) HAI	5.18 (2.35)	5.85 (3.20)

Loss to follow up/reasons:
n=2
Failed to return and were lost to follow-up before 28 weeks

Loss to follow up/reasons:
N=2.
Failed to return and were lost to follow-up before 28 weeks

Effect size

Outcomes- (end of 28 weeks treatment)	Group B: Sequential treatment of LAM followed by Peg IFNa2b (n=34)	Group A: Peg IFNa2b (n=25)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
Undetectable HBV DNA (<4700 copies/ml)	16/34	8/25	0.29
% with ALT normalisation	10/34	5/25	0.55
HBeAg loss	15/34	8/25	0.43
% with HBsAg loss and/or seroconversion	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)		Not reported	Not reported
Incidence of resistance			Not reported

Outcomes (end of 24 weeks follow up)	Group B: Sequential treatment of LAM followed by Peg IFNa2b (n=34)	Group A: Peg IFNa2b (n=25)	p value

Log reduction of HBV DNA	Not reported	Not reported	Not reported
Undetectable HBV DNA (<4.7 copies/ml)	18/34	4/25	0.02
% with ALT normalisation	13/34	5/25	0.15
HBeAg loss	14/34	4/25	0.05
% with HBsAg loss and/or seroconversion	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported
Incidence of resistance	Not reported		Not reported

Authors' conclusion:.
The strategy of using an antiviral initially to decrease HBV DNA levels before adding an immunomodulatory agent leads to improved sustained virological response as compared with using immunomodulator from the start.

Notes: no patient in either group had grade III or IV abnormalities in serum bilirubin levelsm Hb level, neutrophil counts or white cell counts.

Sequential treatment with lamivudine then lamivudine plus interferon alpha combination therapy versus lamivudine alone

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sarin 2005	RCT- unclear blinding Setting: India Computer generated randomisation	N= 75	Treatment naïve HBeAg positive patients with histologically proven chronic hepatitis B and ALT >1.5 ULN Inclusion: Inclusion criteria: adult males and females 16-70 years old, HBsAg positive, HBeAg positive, and anti-HBe antibody negative at the time of screening and for at least the previous 6 months, quantifiable serum HBV	Group A: Sequential therapy of lamivudine 100 mg per oral, once daily for 8 weeks, followed	Group B (monotherapy): Lamivudine 100 mg per oral once daily for 52 weeks	52 weeks treatment plus 24 weeks follow up	Undetectable HBV DNA; loss of HBeAg; HBeAg seroconversion; loss of HBsAg; histological improvement;	None reported

	Allocation concealment unclear. Blinding not reported. ITT used		DNA levels of >1.4x10^5 copies/ml , ALT levels greater than 1.5 times the upper limit of normal and less than 10 times the upper limit of normal at screening and for at least the previous 3 months, liver biopsy proven chronic hepatitis B within previous 12 months of inclusion, and treatment naïve. Exclusion: Exclusion criteria: hepatitis C, D, or HIV infection, decompensated liver disease, evidence of liver disease due to other aetiology, serum creatinine more than 1.5 times upper limit of normal, haemoglobin less than 10g/dl, platelet count less than 70,000/mm^3, white cell count less than 3000/mm^3, serious concurrent medical illnesses and inability to give an informed consent. Baseline characteristics Characteristic: Group A (n=38) / Group B (n=37) age (yrs) mean±SD: 30±12 / 31±16 Sex (% men): 35 (92.1) / 31 (83.3) mean±SD serum HBV DNA (log10 copies/ml: 4.5x10^8± 5.7x10^8 / 6.5x10^8± 7.7x10^8 mean±SD serum ALT IU/L: 116±69 / 114±71 Cirrhosis n (%): 5 (13.6) / 7 (18.9) Mean (SD) HAI: 5.16 (2.33) / 5.84 (3.18) There were no statistically significant differences	by combination of LAM + IFN-α 5 MU daily subcutaneously for 16 weeks followed by LAM alone for 28 weeks (n=38) Total duration of treatment: 52 weeks Loss to follow up/reasons : n=4 before week 52 Two patients withdrew due to side-effects. Two patients failed to return and	(n=37) Total duration of treatment: 52 weeks Loss to follow up/reasons : n=2 before week 52 patients failed to return and were lost to follow-up.		incidence of resistance	

			between the two groups with respect to baseline characteristics.	were lost to follow-up.				

Effect size

Outcomes- 52 weeks	Group A (n=34)	Group A (n=35)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
undetectable HBV DNA	16/34	13/35	0.2
Incidence of resistance	6/34	3/35	NS
n (%) with ALT normalisation	18/34	15/35	0.4
HBeAg loss	15 /34	14 /35	1
HBeAg seroconversion	10/34	5 /35	0.2
Histological improvement (>points increase in the HAI Score)	14/28	12/26	p=0.793
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

Outcomes- (24 weeks follow up)	Group A (n=34)	Group A (n=35)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
undetectable HBV DNA	15/34	6/35	0.03
Incidence of resistance	Not reported	Not reported	Not reported
n (%) with ALT normalisation	15 /34	5 /35	0.01
HBeAg loss	17/34	7 /35	0.02
HBeAg seroconversion	15/34	4/35	0.007
HBsAg loss	1/34	0/35	0.01
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

Authors' conclusion: Sequential therapy is superior to lamivudine monotherapy in achieving sustained seroconversion, ALT normalisation, and HBV DNA loss.

Notes

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hasan 2003	RCT Multicentre : Kuwait Open label study Not details of randomisation . Allocation concealment unclear. ITT analysis	N= 61	HBeAg positive chronic hepatitis B infection and raised ALT. All patients were interferon naïve. Inclusion: Inclusion criteria: age 16-65 years; documented presence of HBsAg for at least 6 months, positive serum HBeAg, HBV DNA level greater than 700,000 copies/ml (2.5pg/ml), serum ALT levels greater than 1.3 times the upper limit of normal, biopsy proven chronic hepatitis within 12 months of inclusion, and compensated liver disease characterised by serum bilirubin ≤30µmol/l, serum albumin ≥30g/L; prothrombin time within 4 seconds over control, and no history of encephalopathy or variceal haemorrhage. Exclusion: Haemoglobin level ≤100g/l, platelet count ≤50,000 per cubic millimetre, white cell count ≤3000 per cubic millimetre. Other exclusion criteria were co-infection with HCV or HDV, serum creatinine ≥140µmol/l, malignancy, sever cardiopulmonary disease, history of immunosuppressive or anti-viral therapy within 12 months of inclusion. Baseline characteristics Characteristic | Interferon +lamivudine (n=32) | Lamivudine (n=29) Median age (range) | 30 (17-63) | 28 (18-60) Nationality n (%) Kuwaiti | 30 (93.8) | 27 (93)	Group A; sequential treatment; patients received interferon alfa 2a, 4.5 million units daily for 5 weeks then a combination of IFNa + LAM (100mg daily) for 11 weeks then LAM alone for 37 weeks weeks (n=32) Total duration of	Group B - Lamivudine (100g daily) (n=29) Total duration of treatment: 48 weeks Loss to follow up/reasons: no loss to follow-up	52 weeks after end of treatment	Undetectable HBV DNA by bDNA assay (lower limit of detection 2.5pg/mL); HBeAg seroconversion; ALT normalisation; safety	None reported

			Mean ±SD serum HBV DNA (pg/ml) 210.4±166.9 235±173 Mean ±SD serum ALT (IU/L) 92.9±21.2 92.8±20.1 Necroinflammatory score median (range) 4 (1-6) 5 (1-6) No statistically significant differences were found between the two groups.	treatment: 53 weeks Loss to follow up/reasons: n=1. Due to severe and persistent flu like symptoms				

Effect size

Outcomes- end of treatment	Sequential treatment (n=31)	Lamivudine (n=29)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
Undetectable HBV DNA	31/31	29/29	Not reported
HBeAg seroconversion	2/31	0/29	Not significant
% with ALT normalisation	29/31	28/29	Not significant
HBsAg loss	Not reported	0	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported
Incidence of resistance	Not reported		Not reported

Outcomes- 52 weeks after stopping therapy	Interferon +lamivudine (n=31)	Lamivudine (n=29)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported

Undetectable HBV DNA	Not reported	Not reported	Not reported
HBeAg seroconversion	2/31	0/29	Not significant
% with ALT normalisation	3/31	2/29	Not significant
Incidence of resistance	Not reported	Not reported	Not reported
HBsAg loss	Not reported	0	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported

Authors' conclusion:.

The sequential administration of interferon plus lamivudine was not superior to lamivudine monotherapy for the treatment of chronic hepatitis B and was associated with more side effects.

Notes:

E.6.3.4 HBeAg positive previously treated with lamivudine patients with CHB

Switching from lamivudine to adefovir versus combination treatment of lamivudine plus adefovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hann 2010	RCT Single centre: USA No details of randomisation and allocation	N= 35	Patients with chronic hepatitis B receiving lamivudine therapy for ≥ 6 months (some lamivudine-resistant) Inclusion: Lamivudine therapy for 6 months or longer regardless of the HBV DNA level, ALT level, HBeAg status, presence or absence of LAM-R by genotyping or viral breakthrough.	Direct switch from lamivudine to adefovir (n=18) Total duration of	Overlap – overlapping lamivudine and adefovir for 3 months followed by adefovir monotherapy (n=17)	3 months and 6 months follow-up [after 12 months therapy	Undetectable HBV DNA by real-time PCR (<160 copies/ml [lower limit of detection]) Viral breakthrough ALT	Gilead Sciences

	concealment reported. Open label		Exclusion: Not reported Baseline characteristics (see table below) There were no significant differences between the groups for baseline characteristics.	treatment: 12 months Loss to follow up/reasons: none	Total duration of treatment: 12 months Loss to follow up/reasons: none	]		

Characteristic	Direct switch (n=18)	Overlap (n=17)
age , mean (SD)	48 (9.6)	43 (10.1)
Sex (% men)	13 (72)	10 (59)
Median serum HBV DNA (range), copies/ml	$1.1x10^4$ ($159-1.1x10^9$)	$8.0x10^4$ ($159-1.5x10^9$)
Median serum ALT (range), U/L	44 (16-266)	33 (19-367)

Effect size

Outcomes (end of 12 months treatment)	Switching from LAM to ADF (n=18)	LAM +ADF followed by ADF (n=17)	p value
HBV DNA <160 copies/ml	9/18	7/17	0.40
Viral breakthrough	0/18	2/17	Not reported

ALT (median)	33 U/L	19 IU/L	Not reported
% with HBeAg loss and/or seroconversion	Not reported	Not reported	Not reported
% with HBsAg loss and/or seroconversion	Not reported	Not reported	Not reported
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported
% withdrawn due to adverse events	Not reported		Not reported

HBV DNA levels (<160 copies/ml at 12 months after adefovir treatment):

No difference was observed between the direct switch (n=18) and overlap (n=17) group with respect to – those with undetectable HBV DNA remaining negative at 12 months (p=0.40) and those who were HBV DNA (+) at baseline and became HBV DNA (-) (p=0.71).

No difference between groups with regard to baseline HBV DNA (p=0.40) and at 12 months (p=0.63) was found.

ALT flare:

No ALT flare was noted in either group at any time point.

Authors' conclusion:.

The study did not show an ALT flare during switch to adefovir at 3 months or at any time later. Neither regimen appeared to be superior for lowering HBV DNA levels at 12 months.

Notes:

E.6.3.5 HBeAg positive lamivudine refractory or resistant patients with CHB

Switching from lamivudine to entecavir versus continuing lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Sherman M et al., 2006	RCT Phase III double-blind, double-dummy, active controlled trial Randomisation: randomised centrally using an interactive voice response system; blocks of permuted treatment assignments, stratified by study site Blinding: Investigators,	N= 286 Lamivudine-refractory, HBeAg positive	Inclusion: men and women aged 16y or older, receiving ongoing lamivudine therapy and were refractory to lamivudine (persistently detectable HBV DNA by bDNA assay after at least 36wk of lamivudine; recurrence of detectable HBV DNA by bDNA assay on 2 determinations after achieving undetectable HBV DNA on lamivudine; recurrence and persistence of HBV replication after discontinuing lamivudine provided that lamivudine had been reintroduced and maintained for at least 12 months prior to screening; or documented YMDD mutation and HBB viraemia). HBeAg(+) and had ALT levels 1.3-10 times the ULN and HBV DNA >=3.0 MEq/ml at screening. Patients had compensated liver function with total serum bilirubin <=2.5mg/dl, prothrombin time <=3 sec longer than the normal control or international normalised ratio <=1.5; serum albumin >=3g/dl; no history of variceal bleeding, ascites requiring diuretics or paracentesis, or encephalopathy. Patients were required to have evidence of CHB upon liver biopsy that was performed at screening or within 1y prior to randomisation and following clinical evidence of incomplete response to lamivudine. Setting: International multi-centre (84 sites; USA, Europe, Middle East, Australia and Asia)	Switching from lamivudine to entecavir (1mg daily)* (n=141) Total duration of treatment: minimum 52 weeks Loss to follow up/reasons: 8 did not complete 52 weeks treatment (2 lost to F/U, 2 withdrew consent, 1 adverse event, 3	Continuing lamivudine (100mg daily)* (n=145) Total duration of treatment: minimum 52 weeks Loss to follow up/reasons: 19 did not complete 52 weeks treatment (1 lost to F/U, 5 withdrew consent, 8	up to week 48 on treatment	Primary: histological improvement (≥2 point decrease in Knodell necroinflammatory score and no worseining of fibrosis score at week 48; HBV DNA <0.7MEq/mL by bDNA assay and ALT <1.25 x ULN at week 48 Secondary: mean log_{10} reduction of HBV DNA from baseline % with undetectable HBV DNA by	not stated

	patients and study sponsor were blinded to results and treatment assignments until week 52 Sample size calculation provided: 135 per group provided 90% power to detect superiority of entecavir assuming a 25% response rate for lamivudine and ≥50% for entecavir, 25% missing data and 2-sided significance of 0.025		Exclusion: co-infection with hepatitis C, D or HIV; other forms of liver disease; prior therapy with a nucleos(t)ide analogue with activity against HBV other than lamivudine for >=12weeks duration or given within 6 months prior to randomisation; use of IFN alpha or thymosin-alpha-1 within 6 months prior to randomisation; alpha-fetoprotein >100ng/ml; and prior treatment with entecavir Baseline characteristics Entecavir (n=141) / Lamivudine (n=145) Mean age (range): 38 (16-74) / 40 (17-70) Male (%): 105 (74) / 112 (77) Sex (% men) Mean serum HBV DNA by PCR (SD), log10 copies/ml: 9.48 (1.81) / 9.24 (1.56) Mean serum ALT (SD), U/L: 123.9 (109.72) / 131.9 (165.11) HBeAG positive n (%): 136 (96) / 142 (98) Race (%) White: 83 (59) / 93 (64) Asian: 57 (40) / 50 (34) Other: 1 (<1) / 2 (1) Viral genotype (%) A B: 37 (26) / 32 (22) C: 23 (16) / 17 (12) D: 27 (19) / 28 (19)	non-compliance); of these, one patient had 48 week outcomes Among the 133 patients who completed the 52 week treatment, 132 had 48 week outcomes. *No interruption in lamivudine therapy before randomisation	adverse events, 1 non compliance, 1 did not meet criteria, 2 treatment failure, 1 death); of these, 9 patients had 48 week outcomes Among the 126 patients who completed the 52 week treatment, 120 had 48 week outcomes.		PCR assay (lower limit of detection <300 copies/ml) % with ALT normalisation (≤1 x ULN) % with HBeAg loss % with HBeAg seroconversion (HBeAg loss and appearance of anti-HBe) Discontinuation due to adverse events All outcomes were assessed at week 48	

			F	45 (32) 4 (3)	56 (39) 3 (2)					
			Mean Knodell necoinflammatory score (SD)	6.5 (3.23)	6.5 (3.41)					
			Mean Knodell fibrosis score (SD)	1.7 (1.19)	1.8 (1.18)					
			Cirrhosis (%)	10	6					
			Prior IFN (%)	74 (52)	80 (55)					

Effect size (Modified ITT analysis – included all randomised patients who received at least 1 dose of study medication and patients with missing measurements at week 48 were counted as failures (non-completer))

Post-treatment (week 48)	Entecavir (1 mg/day) (n=133 with data)	Lamivudine (100 mg/day) (n=129 with data)	p value
Histological improvement of those with evaluable biopsy specimens n (%)	68/124 (55%)	32/116 (28%)	p<0.0001
Mean Log10 reduction of HBV DNA from baseline by PCR assay, log10 copies/ml (SD)	5.11 (2.234)	0.48 (1.972)	<0.0001
% with undetectable HBV DNA (<0.7MEq/mL by bDNA assay)	93/133	8/129	
% with undetectable HBV DNA (<300 copies/ml) by PCR (SD)	27/133	2/129	<0.0001
Incidence of resistance	-	-	
% with ALT normalisation	86/133	22/129	<0.0001
% with HBeAg loss	14/133	5/129	0.278
% with HBeAg seroconversion (HBeAg loss and appearance of anti-HBe)	11/133	4/129	0.06
% with HBsAg loss and/or seroconversion	-	-	--

Quality of life measures (EQ-5, SF-35, liver disease specific)	-	-	--
% withdrawn due to adverse events*	2/141 (1)	10/145 (7)	--

*mean exposure to study therapy was 63 weeks for entecavir vs 52 weeks for lamivudine

Authors' conclusion:. In patients with lamivudine-refractory CHB, switching to entecavir provides superior histologic improvement, viral load reduction, and ALT normalisation compared with continuing lamivudine, with a comparable adverse event profile.

Notes: incidence of resistance. Other results reported: composite end point (HBV DNA <0.7 MEq/ml by bDNA assay and ALT <1.25 x ULN); any/serious SE, ALT flares and death

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chang 2005A	RCT- double blinded multicenter multinational study - randomization method and allocation concealment adequate by using a centralized interactive	N= 87 (the study also included two additional groups of switching from LAM to ETV 0.5 mgr/day and to	Inclusion: Male and female adults (over 16 years) with chronic HBV infection, both HBeAg positive (68%) and negative, who were lamivudine refractory on the basis of documented viremia after receiving at least 24 weeks of lamivudine therapy or documented evidence of a lamivudine reistance associated substitution while receiving lamivudine. Viremia was defined as HBV DNA levels>=10pg/ml by the Abbott column-based hybridization assay, >=25 pg/ml by the Digene chemiluminescent molecular hybridization assay or >=10 Meq/ml by the Chiron b DNA assay on 2 determinations at least 2 weeks apart. ALT ≤10 x ULN and well compensated liver function (prothrombin <3s longer than normal or INR ≤2.23; serum albumin ≥3.0g/dL; total bilirubin ≤2.5mg/dL).	Switching from LAM to ETV 1 mg/day (n=42) Total duration of treatment: up to 76 weeks Loss to follow up/reasons:	Continuing LAM (100mg/day) (n=45) Total duration of treatment: up to 76 weeks Loss to follow up/reasons:	No follow up	1) % with undetectable HBV DNA (<400 copies/ml) 2)% with ALT normalisation 3)% with HBeAg loss 4)% with HBeAg seroconversion	No details.

	voice randomization system (which was stratified by centre)	ETV 0.1mgr/day which were not included in the review as they used lower doses that the one recommended)	Exclusion: Patients coinfected with hepatitis C virus, delta virus, or human immunodeficiency virus, had another form of liver disease or liver transplant, had received immunomodulatory therapy within 24 weeks before randomization, or had received antiviral therapy with nucleosided or nucleotide analogues other than lamivudine for more than 4 weeks. For women of childbearing potential, pregnancy was also an exclusion criterion. Baseline characteristics			2 by week 24 (AE/lab abnormality); further 1 by week 48 (adverse event)	2 by week 24 (lost to follow up); further 16 by week 48 (14 insufficient response withdrawn according to protocol – could have open label entecavir plus lamivudine, or treated at physician's discretion)			

	Switching from LAM to ETV (1 mgr/day) (N=42)	Continuing L (N=45)
Median age (range)	48 (13)	48 (15)
Mean weight (SD), kg	77 (15)	77 (20)
Sex (% men)	39 (93%)	34 (76%)
HBeAg positive	27 (64%)	32 (71%)
Mean (SD) serum HBV DNA, log10 copies/ml	2.48 (0.98)	2.41 (0.87)
Mean serum ALT (SD), U/L	141 (186)	110 (97)
LAM reistance substitution, n (%)	38 (90%)	39 (87%)
HBV genotype -D	-14 (33%)	-14 (31%)

			-A - C -B -other	-13 (31%) -8 (19%) -5 (12%) -2 (4%)	-18 (40%) -8 (18%) -5 (11%) -0 (0%)					

Effect size

Post-treatment (after 24 weeks blinded treatment)	Switching from LAM to ETV (1 mg/day) (N=39*)	Continuing LAM (N=27*)	p value
Log reduction of HBV DNA	4.21 (0.26)	0.95 (0.25)	p<0.001
% with undetectable HBV DNA by bDNA assay (<0.7MEq/mL)	/40	43	0.001
Incidence of resistance	-	-	
% with ALT normalisation (of those with abnormal baseline)	11/28	7/33	--
% with HBeAg loss	-	-	--
% with HBeAg seroconversion	-	-	
% with HBsAg loss and/or seroconversion	-	-	--
Quality of life measures (EQ-5, SF-35, liver disease specific)	-	-	--

* It refers to number of people completed and not randomized

Authors' conclusion:.In HBeAg positive and negative lamivudine refractroy patients, treatment with entecavir 1mg daily was well tolerated and resulted in significant reductions in HBV DNA levels and normalization of alanine aminotransferase levels.

Notes: The majority of viral samples (87%) had evidence of lamivudine resistance associated substitutions at study entry.

Switching from lamivudine to telbivudine versus continuing lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Safadi 2011	RCT Multicentre (40 centres) Randomised using interactive voice recognition system Double blind ITT used Sample size 240 required to provide >90% power to detect a 1 log_{10} copies/mL increment in HBV DNA	N= 246	Chronic hepatitis B patients who exhibited persistent viraemia under lamivudine therapy. HBeAg (+) and HBeAg (-) patients. Inclusion: Male and female adult chronic hepatitis B patients (ages 18-70 years) with HBeAg positive or HBeAg negative compensated liver disease. Key inclusion criteria were prior lamivudine therapy for 12-52 weeks, serum HBV DNA >3 log_{10} copies/ml and serum ALT <10 times the upper limit of normal. Exclusion: Patients were excluded if they had co-infection with hepatitis C, D or HIV; evidence of hepatic decompensation, pancreatitis or HCC; previous treatment for chronic hepatitis with nucleos(t)ide analogues except lamivudine; treatment with interferon-α or other immunomodulators within the past 12 months; other forms of liver disease; serum creatinine level ≥1.5 mg/dl; prothrombin time >3s; serum albumin level <3.3 g/dl; or total bilirubin level ≥2 mg/dl. Eligible patients with a serum α-feto protein >50 ng/ml required exclusion owing to the possibility of underlying HCC.	Switch to Telbivudine 600 mg/day for 52 weeks. (n=122) [all patients previously treated with lamivudine for 12-52 weeks] Loss to follow up/reasons: n=6 [n=2 non-compliance, n=1 adverse events, n=3 patient request]; 116 completed	Continue lamivudine treatment 100 mg/day for 52 weeks (n=124) [all patients previously treated with lamivudine for 12-52 weeks] Loss to follow up/reasons: n=8 [n=1 due to adverse events, n=6 patient request, n=1 death] 116 completed	Weeks 24 and 52 on treatment, no follow up	Log reduction in serum HBV DNA levels from baseline (log_{10} copies/ml); % patients with undetectable HBV DNA by PCR (lower limit of detection <300 copies/mL); ALT normalisation; HBeAg loss; HBeAg seroconversion; virological breakthrough; adverse events; genotypic resistance	Novartis Pharma

reduction with a drop out rate of 10%

Baseline characteristics

	Switch to Telbivudine 600 mg/day. (n=122)	Continue lamivudine 100 mg/day (n=124)
age mean (SE)	35.5 (1.0)	37.3 (1.0)
weight mean (SE), kg	71.2 (1.5)	71.5 (1.24)
Sex (% men)	90 (74)	96 (77)
HBeAg status HBeAg positive HBeAg negative	 81 (66) 41 (34)	 81 (65) 43 (35)
Median serum HBV DNA , log_{10} copies/ml	5.0	5.3
serum ALT mean (SE), IU/L	68.5 (7.1)	57.7 (4.8)
Duration of prior lamivudine therapy (years) mean (SE)	0.6 (0.03)	0.5 (0.03)
Caucasian Asian Korean African/African-American Middle Eastern/Indian Other	15 (12) 75 (61) 55 (68) 13 (16) 0 25 (20) 7 (6)	13 (10) 76 (61) 63 (80) 12 (15) 2 (2) 29 (23) 4 (3)

Effect size

Outcomes- week 52 (ITT last observation carried forward)	Switch to Telbivudine 600 mg/day. (n=122)	Continue lamivudine treatment 100 mg/day (n=124)	Comparison
Log reduction of HBV DNA (log 10 copies/ml)[mean (SE)]	-1.5 (0.28)	-0.1 (0.31)	p<0.001
Undetectable HBV DNA (<300 copies/mL) - n/N (%) HBeAg positive HBeAg negative	56/121 28/81 28/40	38/124 12/82 26/42	p=0.005
Incidence of resistance	Not reported	Not reported	
ALT normalisation- n/N (%)	32/53 (60)	27/53 (51)	p=0.202
HBeAg loss -n/N (%)	15/81 (19)	11/81 (14)	p=0.277
HBeAg seroconversion- n/N (%)	12/81 (15)	8/81 (10)	p=0.095
Virological breakthrough All patients Patients with wild type HBV at screening	 18/122 13/101	 20/124 19/106	 NS
Genotypic resistance All patients Patients with wild type HBV at screening	 15/101 (15/18 with breakthrough) 12/101	 13/124 (13/20 with breakthrough) 13/106	NS
% withdrawn due to adverse events	1/122	1/124	

Authors' conclusion:
Early (≤ 24 weeks) switch to Telbivudine improved virological outcomes in chronic hepatitis B patients with persistent viral replication under lamivudine treatment.

Notes:

Switching from lamivudine alone to combination treatment of lamivudine plus adefovir versus switching from lamivudine to entecavir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ryu 2010	Unblinded RCT in Korea -no details on randomization method or allocation concealment	N= 92	Lamivudine resistant Inclusion: Patients older than 16 years who had received lamivudine treatment for at least 6 months, had a serum HBV DNA ≥10^5 copies/ml as detected by PCR, and were confirmed to have the YMDD mututation. Exclusion: Decompensated cirrhosis (history of ascites, encephalopathy, varices, serum total bilirubin >2.5 mg/dl, serum albumin <3 mg/dl, or prothrombin time>3 sec longer than normal, serum creatinine level >1.5 mg/dl, previous antiviral treatment other than lamivudine, treatment with immunomodulatory drugs, current corticosteroid usage, coinfection with hepatitis C or HIV, serious concurrent medical illness, evidence of HCC or prior organ transplantation, and poor compliance. Baseline characteristics [see table below]	Switching from lamivudine to lamivudine 100mg plus adefovir 10mg (n=47) Total duration of treatment: mean 12 months Loss to follow up/reasons: no information provided	Switching from lamivudine to entecavir 1mg (n=45) Total duration of treatment: mean 15 months Loss to follow up/reasons: no information provided	12 months of treatment; no follow up	1) Log reduction of HBV DNA 2) % with undetectable HBV DNA (<300 cpoies/mL by PCR) 3)% with ALT normalisation 4)% with HBeAg loss 5)% with HBeAg seroconversion 6) Virological breakthrough 7) Incidence of resistance	Good Health R&D Project Ministry of Health and Welfare, Republic of Korea

Baseline characteristics

	Switching from lamivudine to lamivudine plus adefovir (n=47)	Switching from lamivudine to entecavir (n=4
Median age (range)	47 (20-68)	41 (21-60)
HBeAg positive	39 (83%)	42 (93.3%)
Sex (% men)	34 (72.3%)	38 (84.4%)
Median serum	7.61 (5.19-9.49)	7.1 (5.43-9.47

HBV DNA (range), log10 copies/ml		
Median serum ALT (range), U/L	143 (26-1096)	102 (17-677)
Genotype C	100%	100%
YMDD mutations	47(100%)	45 (100%)
Median (range) prior duration LAM treatment (months)	27 (9-108)	27 (9-81)
Cirrhosis n (%)	9 (19.1)	11 (24.4)

Effect size

Post-treatment (end of 12 months)	Switching from lamivudine to lamivudine plus adefovir (n=47)	Switching from lamivudine to entecavir (n=45)	p value
Log reduction of HBV DNA, mean (SD)	3.8 (1.12)	2.72 (1.32)	<0.001
% with undetectable HBV DNA (<300 copies/ml)	18/47 (38.3%)	11/45 (24.4%)	0.182
Incidence of resistance	0/47	2/45 (4.4%)	-
% with ALT normalisation	39/41 (95.1%)	36/40 (90%)	0.432
% with HBeAg loss	4/39 (10.3%)	2/42 (4.8)	0.421
% with HBeAg seroconversion	2/39 (5.1%)	1/42 (2.4%)	0.606
Virological breakthrough n (%)	1 (2.1)	5 (11.1)	0.107
Quality of life measures (EQ-5, SF-35, liver disease specific)	-	-	--
% withdrawn due to adverse events	not stated		

Authors' conclusion: Compared with switching to ETV monotherapy, adefovir added to lamivudine therapy was more effective at reducing the viral load in patietns with LAM resistance, and the baseline HBV DNA and ALT levels were independent predictors of the virologic response.

Notes:

Switching from lamivudine plus adefovir to entecavir plus adefovir versus continuing lamivudine plus adefovir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lim 2012	RCT randomization method: simple randomisation using block size of 6 by independent statistician allocation concealment: adequate open label	N=90	Inclusion: men and women aged 16-75 years; HBsAg positive for at least 6 months and positive or negative for HBeAg; confirmed mutations conferring resistance to lamivudine; serum HBV DNA >2000 IU/mL after combination treatment with LAM (100mg/day) plus ADV (10mg/day) for at least 6 months; well-preserved liver function (Child-Pugh-Turcotte score ≤6); no history of ascites, variceal bleeding or encephalopathy. Exclusion: previous or current hepatocellular carcinoma; prior antiviral treatment other than LAM and/or ADV, coinfected with hepatitis C, D or HIV, creatinine >1.5mg/dL, concurrent systemic corticosteroids or othe rimmunosuppressants, history of alcohol or substance abuse, pregnant, breast-feeding or planning pregnancy, other concurrent liver	Switching from lamivudine + adefovir to entecavir 1mg daily orally + adefovir 10mg daily orally (ETV + ADV group) (n=45) Total duration of treatment: 52 weeks	Continuing on lamivudine 100mg daily orally + adefovir 10mg daily orally (LAM + ADV group) (n=45) Total duration of treatment: 52 weeks Loss to	52 weeks treatment; no follow up	Primary: virologic response (HBV DNA <60IU/mL) at week 52 Secondary: changes in serum HBV DNA, normal ALT, HBeAg loss, resistance mutations to ADV and ETV at week 52	Bristol-Myers Squibb

	single centre in South Korea sample size calculation: 45 patients per group had 85% power to detect a 33% success rate for LAM + ADV versus 65% for ETV + ADV with p=0.05 and a drop out rate of 5%		disease, prior organ transplantation, history of malignancy within 3 years Baseline characteristics	Loss to follow up/reasons: 0	follow up/reasons: 0			

	ETV + ADV group (n=45)	LAM + ADV group) (n=45)
Mean (SD) age years	44.9 (11.4)	48.8 (11.4)
HBeAg positive n (%)	39 (86.7)	41 (91.1)
Sex n (%) men	33 (73.3)	34 (75.6)
Median serum HBV DNA (IQR), log_{10} copies/ml	4.40 (3.59-5.18)	4.60 (3.93-5.25)
Median serum ALT (IQR), IU/L	28 (19-40)	33 (25-47)
Cirrhosis n (%)	14 (31.1)	13 (28.9)
Median (IQR) duration of prior LAM + ADV therapy (months)	12 (7-39)	17 (6-37)
LAM resistance mutations n (%)	45 (100)	45 (100)
ADV resistance mutations n (%)	7 (15.6)	12 (26.7)

Effect size

Post-treatment (52 weeks)	ETV + ADV group (n=45)	LAM + ADV group (n=45)	Comparison

Reduction of HBV DNA, mean (SD) log $_{10}$ IU/mL	2.24 (1.30)	0.64 (0.83)	p<0.001
% with undetectable HBV DNA (<60 IU/ml)	13/45 (28.9%)	2/45 (4.4%)	p=0.004
Virological breakthrough	0/45	1/45	
Resistance mutation to ADV or ETV n (%)	3 (6.7)	15 (33.3%)	p=0.003
% with ALT normalisation	26/45 (57.8)	20/45 (44.4)	NS
% with HBeAg loss	2/39 (5.1)	0/41 (0)	NS
% with HBeAg seroconversion	0	0	
Quality of life measures (EQ-5, SF-35, liver disease specific)	not reported	not reported	
% withdrawn due to adverse events	none		

Authors' conclusion: Entecavir plus adefovir combination therapy provides superior virologic response and favourable resistance profiles compared with the continuing lamivudine plus adefovir combination in patients with lamivudine-resistant HBV who fail to respond to lamivudine plus adefovir combination therapy.

E.6.3.6 HBeAg negative patients with chronic hep B responders to previous treatment with lamivudine

Switching from lamivudine to entecavir versus continuing lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding

Matsuura 2011	RCT RCT of lamivudine to entecavir switching in chronic hepatitis B responders. Setting: Multicentre (11 institutions in Japan) No details of randomisation. Allocation concealment unclear. Blinding not reported. completers analysed	N= 27	Adult patients treated with lamivudine for more than 3 years (median 50 months, range 36-106 months), who showed HBV DNA of less than 2.6 log copies/ml at entry. Majority HBeAg (-). Inclusion: Before starting lamivudine administration, all patients were positive for hepatitis B surface antigen (HBsAg) in serum, abnormal ALT, detectable for HBV DNA, and were not infected with hepatitis C and HIV. Exclusion: Patients diagnosed with alcoholism, primary biliary cirrhosis or autoimmune hepatitis were excluded. Baseline characteristics <table><tr><th>Completers</th><th>Lamivudine (n=15)</th><th>Entecavir (n=11)</th><th>p-value</th></tr><tr><td>age (yrs) mean ±SD</td><td>53±7</td><td>57±7</td><td>Not significant</td></tr><tr><td>men</td><td>10</td><td>6</td><td>Not significant</td></tr><tr><td>Prior duration of lamivudine administration (months)</td><td>59±23</td><td>55±18</td><td>Not significant</td></tr><tr><td>HBeAg positive n (%)</td><td>1(6%)</td><td>1 (8%)</td><td>Not significant</td></tr><tr><td>ALT (IU/L)</td><td>33±29</td><td>28±22</td><td>Not</td></tr></table>	Switching to Entecavir 0.5 mg/day (n=12) [switching to entecavir group] Duration of treatment in this study: 2 years Loss to follow up/reasons: n=1 Drop-out due to skin rash side-effect	Lamivudine 100mg/day (n=15) [lamivudine continued group] Duration of treatment in this study: 2 years Loss to follow up/reasons: no loss to follow-up	Mean follow-up 24±3 months (on treatment)	Primary: viral breakthrough (VBT) or breakthrough hepatitis (BTH) Incidence of resistance % patients with undetectable HBV DNA by Amplicor HBV Monitor (lower limit of detection <2.6 log copies/ml) or COBAS AmpliPrep-COBAS TaqMan HBV test (lower limit of detection 2.1 log copies/mL)	Grant-in-aid from the Ministry of Education, Culture, Sports, Science and Technology.

			mean ±SD			significant			

There was no difference in sex, age, duration of lamivudine administration and ALT level between the two groups.

Effect size

Outcomes- Mean treatment period 24±3 months	Switching to ETV (n=11)	Continuing LAM (n=15)	p value
Breakthrough hepatitis	0	0	
Virological breakthrough	0/11	6/15	Not reported
Incidence of resistance	0/11	6/15	0.02
Undetectable HBV DNA (<2.6 log copies/ml)	5/11	5/15	Not reported

Authors' conclusion:

In patients treated with lamivudine for more than 3 years maintaining HBV DNA less than 2.6 log copies/ml, switching treatment to entecavir is recommended at least during the 2 years follow-up period.

Notes:

E.6.3.7 HBeAg negative patients with CHB previously treated with entecavir and undetectable HBV DNA

Switching from entecavir to lamivudine alone versus continuing entecavir

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Fung 2011	A prospective RCT in Hong Kong - randomization method using computer generated numbers - blinding unclear -allocation	N= 50	Inclusion: Patients previously treated with entecavir 0.5mg for at least 6 months and undetectable HBV DNA (<60 copies/ml) and normal alanine aminotransferase (ALT) after initital ETV treatment. Exclusion: Elevated ALT or detectable viral load ; evidence of hepatocellular carcinoma or history of decompensated liver cirrhosis. Baseline characteristics Switching from / Continuing entecavir	Switching from entecavir to lamivudine 100mg daily (n=25) Protocol stated that patients were to be switched back to entecavir	Continuing entecavir 0.5mg daily (n=25) Total duration of treatment: 96 weeks Loss to follow up/reasons:	96 weeks on treatment; no follow ups	Primary: virological rebound Secondary: drug-resistant mutation; biochemical flare % with undetectable HBV DNA by	Lamivudine supplied by GlaxoSmithKline

	concealment inadequate Sample size: 38 patients required for a two-sided significance level of 0.05 and a power of 80% to detect a difference between the resistance rates at 2 years of 1% with entecavir and 35% with lamivudine			entecavir to lamivudine (n=25)	(n=25)	0.5mg if evidence of virological rebound [single HBV DNA level >100 copies/mL [20IU/mL] or persistent HBV DNA levels 60-100 copies/mL [12-20 IU/mL] on 3 consecutive samples taken 2 weeks apart] with lamivudine: Total duration of treatment: 96 weeks	0; no rebound		Cobas TaqMan (lower limit of detection 60 copies/mL [12IU/mL]) % with ALT normalisation (<53 U/L for males and <31 U/L for females)	
				Median age (range)	50 (22-62)	49 (23-56)				
				Cirrhosis (%)	1 (4%)	3 (12%)				
				Sex (% men)	16 (64%)	20 (80%)				
				Median serum HBV DNA (range), l copies/ml	<60	<60				
				Median serum ALT (range), U/L	22 (13-38)	27 (12-45)				
				HBeAg postivie	4 (16%)	5 (20%)				
				Length of prior ETV (months)	13 (6-25)	11 (6-24)				
				Duration of prior entecavir (months)	13 (6-25)	11 (6-24)				

Effect size

Post-treatment (end of 96 weeks	Switching from entecavir to lamivudine	Continuing entecavir (n=25)	p value

treatment)	(n=20)		
Virological rebound	6 had rebound (4 switched to entecavir; 1 continued on lam; 1 had adefovir added)		
Log reduction of HBV DNA	-	-	--
% with undetectable HBV DNA (<100 copies/ml)	19/25	25/25	--
Incidence of resistance	3/20	0/25	
% with ALT normalisation	20/20	25/25	--
% with HBeAg loss and/or seroconversion	-	-	--
% with HBsAg loss and/or seroconversion	-	-	--
Quality of life measures (EQ-5, SF-35, liver disease specific)	-	-	--

-

Authors' conclusion: Sequential therapy using entecavir followed by lamivudine resulted in virological rebound in 24% of patients after 96 weeks. Prior optimal viral suppresion with entecavir did not confer any significant advantage in patients who switched to lamivudine.

Notes: There sample size was calculated at 38 using a 2-sided significance level of 0.05, a desired power of 0.80 and an estimated entecavir and lamivudine resistance rate at 2 years of 1% and 35% respectively. There were no new symptoms and no serious adverse events in either arm to 96 weeks of follow up.

E.6.4 Sequential treatment for children with CHB

E.6.4.1 Interferon alpha (6 months) vs sequential treatment of lamivudine alone (2 months) followed by interferon alpha plus lamivudine (6 months) followed by lamivudine alone (4 months)

See below (Dikici 2004; three-armed trial)

E.6.4.2 Interferon alpha vs sequential treatment of interferon alpha plus lamivudine (6 months) followed by lamivudine alone (6 months)

E.6.4.3 See below (Dikici 2004; three-armed trial)

E.6.4.4 Switching from interferon alpha plus lamivudine (6 months) to lamivudine alone(6 months) versus sequential treatment of lamivudine alone (2 months) followed by interferon alpha plus lamivudine (6 months) followed by lamivudine alone (4 months)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Dikici 2002	RCT- unclear blinding Randomisation inadequate: the patients were	N=32	Children with chronic hepatitis B infection aged between 4 and 14 years. Inclusion: Inclusion criteria were the presence of hepatitis B surface antigen (HBsAg) in serum for at least 6 months, presence of hepatitis B early antigen (HBeAg), absence of HBsAg antibody (anti-HBs), absence of HBeAg	Group 1 (n=17) INF-α 10 MU/m^2 and lamivudine 4mg/kg	Group 2 (n=15) Lamivudine 4mg/kg (max 100 mg) was started	End of 12 months and 18 months of treatme	Complete response at the end of therapy: HBeAg/anti-HBe seroconversion, clearance of	Not reported

	randomly allocated to either study group consecutively but more than one child in the same family was gathered in the same group; no details of allocation concealment.. Setting-Turkey		antibody (anti-HBe), ALT values more than 1.5 times the normal upper limit (ULN:40 IU/L), presence of HBV DNA, histological evidence of chronic hepatitis on liver biopsy taken within 6 months of enrollment, no previous use of nucleoside analogues or INF-α for chronic HBV infection, absence of co-infection with hepatitis C virus, hepatitis D virus or HIV, decompensated cirrhosis, and no other causes of chronic liver diseases. Exclusion: Exclusion criteria were age less than 2 years, platelet count <150.000/mm^3, leukocyte counts <3000/mm^3 , haemoglobin levels below 10g/dl, existence of epilepsy or serious central nervous system diseases, psychiatric disorders, kidney insufficiency and hepatic decompensation. Baseline characteristics Group 1 (n=17) / Group 2 (n=15) / p-value Mean age (years): 8.7±2 / 7.9±2 / NS Sex (% female): 18 / 13 / NS HBV DNA 1000-2000 pg/ml: 2 / - / NS HBV DNA >2000 pg/ml: 15 (88%) / 15 (100%) / NS Mean (SD) serum ALT IU/L: 125±100 / 111±63 / NS No. of pts: 8 / 8 / NS	(max 100 mg) given simultaneously for 6 months. Then lamivudine alone continued for 6-12 months. Total duration of treatment: 12-18 months Loss to follow up/reasons: No loss to follow-up	alone for the first 2 months, with INF-α 10 MU/m^2 added to lamivudine throughout the following 6 months. Then IFN-α was stopped after 8 months and lamivudine alone was continued for 4 months. The same doses of lamivudine and INF-α were used in both groups. Total duration of treatment:12 months Loss to follow up/reasons:	nt; 6 motnhs follow up afterwards	HBV DNA and normalization of ALT. Sustained response = same criteria 6 months after end of treatment clearance of HBsAg clearance of HBeAg seroconversion to anti-HBs seroconversion to anti-HBe normalisation of ALT (IU/ml)	

			with ALT >100					No loss to follow-up			
			Mean (SD) HAI	6.5 (2.4)	7.1 (2.7)	NS				
			There were no significant differences between the two groups in for any of the baseline characteristics.							

Effect size

	INF-α and lamivudine 6 months then lamivudine alone 6-12 months (n= 17)	Lamivudine alone 2 months then INF-α + lamivudine for 6 months then lamivudine alone for 4 months (n=15)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported
% with undetectable HBV DNA at end of therapy	16/17	14/15	Not reported
% with undetectable HBV DNA 6 months after end of therapy	16/17	12/15	Not reported
Incidence of resistance	Not reported	Not reported	Not reported
ALT normalisation at end of therapy n (%)	14/17 (82%)	11/15 (73%)	NS
ALT normalisation 6 months after end of therapy	14/17 (82%)	10/15 (67%)	NS
Mean (SD) ALT IU/L at 12 months	28±8 (p<0.05 vs. baseline)	35±2 (p<0.05 vs. baseline)	NS
Mean (SD) ALT IU/L at 18 months	36±37 (p<0.05 vs. baseline)	34±2 (p<0.05 vs. baseline)	NS
Clearance of HBsAg, n (%) at 12 months	4 (23)	3 (20)	NS
Clearance of HBsAg, n (%) at 18 months	4 (23)	3 (20)	NS
Clearance of HBeAg, n (%) at 12 months	11 (65)	9 (60)	Not reported
Clearance of HBeAg, n (%) at 18 months	11 (65)	8 (53)	Not reported
Seroconversion to anti-HBs, n (%) at 12 months	3 (17)	2 (13)	NS
Seroconversion to anti-HBs, n (%) at 18 months	3 (17)	2 (13)	NS
Seroconversion to anti-HBe, n (%) at 12 months	8 (47)	6 (40)	Not reported
Seroconversion to anti-HBe, n (%) at 18 months	8 (47)	7 (46)	Not reported
Complete response at the end of therapy: HBeAg/anti-HBe seroconversion, clearance of HBV DNA and normalization of	8/17 (47%)	6/15 (40%)	NS

ALT.			
Sustained response 6 months after the end of therapy: HBeAg/anti-HBe seroconversion, clearance of HBV DNA and normalization of ALT.	8/17 (47%)	7/15 (46%)	NS
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported
% withdrawn due to adverse events	Not reported		Not reported

Notes:

Patients tolerated the treatment well. Therapy did not have to be discontinued because of common mild side effects including influenza like symptoms, weakness and gastrointestinal symptoms. None of the children developed hyperamilazemia or unexpected biochemical changes. No child developed severe neutropenia, thrombocytopenia or any other complication of bone marrow suppression.Authors' conclusion: Comparison of two different combination regimens disclosed similar results in the normalisation of ALT, clearance of HBeAg and HBV DNA and seroconversion to anti-HBe. However, the most beneficial combination of lamivudine and IFN- α treatment modalities needs to be further investigated.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Dikici 2004	RCT- unclear blinding Multi-centre study in Turkey (11 centres) No details of randomisation and	N=182	Children with Chronic hepatitis B aged between 3 and 15 years Inclusion: Inclusion criteria included the presence of HBsAg in serum for at least 6 months; presence of HBeAg; absence of hepatitis Be antibody (anti-HBe); ALT values more than 1.5 fold the normal upper limit (40 IU/L); presence of HBV DNA and histological evidence of chronic hepatitis on liver biopsy taken within 6 months of enrollment; no previous use of nucleoside	Group 1: IFN-α 2b ($10MU/m^2$) thrice weekly (n=62) Total duration of treatment: 6 months	Group 2: IFN-α ($5 MU/m^2$) three times a week for 6 months + lamivudine (4 mg/kg, maximum 100 mg/day) for 6 months	6 or 12 months treatment plus follow up to a total of 24 months	Clearance of HBeAg HBeAg seroconversion - ALT normalisation Clearance of HBV DNA Clearance of HBsAg and	Not reported

	allocation concealment.		analogues or IFN-α for chronic HBV infection; absence of co-infection with hepatitis C virus; hepatitis delta virus or HIV; absence of decompensated cirrhosis and any other causes of chronic liver disease. Exclusion: Exclusion criteria were age <2 years; platelet count <150000 /mm^3; haemoglobin level <10 g/dl; existence of epilepsy or serious central nervous system diseases; psychiatric disorders; kidney insufficiency or hepatic decompensation. Baseline characteristics [table]	Loss to follow up/reasons: not reported	followed by lamivudine alone for 6 months (n=60). Total treatment time 12 months Group 3: Lamivudine (4 mg/kg, maximum 100 mg/day) was started alone for the first 2 months and IFN was added to lamivudine for 6 months, then IFN was stopped at 8 months and lamivudine alone was continued for 4 months). (n=60)		seroconversion of anti HBs % Complete response at the end of therapy: HBeAg/anti-HBe seroconversion, clearance of HBV DNA and normalization of ALT. Sustained response = same criteria 6 months after end of treatment	

	Group 1: IFN-α (n=62)	Group 2: IFN-α+ lamivudine (n=60)	Group 3: IFN-α+ Lamivudine (n=60)
Mean±SD age	7.4±3.8	8.8±3.7	10.5±9.0
Sex (% male)	58	55	70
Mean ± SD serum ALT (IU/L)	109.2±93.6	101.7±53.7	103.1±68.9
Mean (SD) HAI	9.0 (3.1)	8.0 (3.0)	7.6 2.5)
HAI (n): Mild (5-8 points) Moderate (9-12) Severe	 13 10	 12 13	 16 13

			(13-18) 39 29 31 There were no significant differences between the treatment groups for baseline characteristics.		Total duration of treatment: 12 months Loss to follow up/reasons: not reported				

Effect size

Post-treatment (end of treatment)	Group 1: IFN-α for 6 months (n=62)	Group 2: IFN-α+ lamivudine for 6 months followed by lamivudine alone for 6 months (n=60)	Group 3: Lamivudine for 2 months then LAM plus IFN for 6 months, then lamivudine alone for 4 months (n=60)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported	Not reported
Undetectable HBV DNA n (%)	21/62 (33.8%)	53/60 (87.7%)	56/60 (93.5%)	reported<0.05 between group 1 and the others; group 2 and 3 NS
Incidence of resistance	Not reported	Not reported	Not reported	Not reported
Mean (SD) ALT IU/L	82 (111) (p=0.046 vs. group 2 and p=0.002 vs. group 3)	38 (41) (NS vs. group 3)	29 (16)	p<0.05
% with ALT normalisation	Not reported	Not reported	Not reported	Not reported
HBeAg seroconversion n (%)	14/62 (22.5%)	26/60 (44%)	21/60 (35%)	NS
HBeAg loss n (%)	16/62 (25%)	31/60 (51.7%)	26/60 (43.3%)	Not reported
Clearance of HBsAg and seroconversion of anti-HBs %	3/62 (4.8%)	7/60 (11.8%)	5/60 (8.4%)	NS
Complete response at the end of therapy: HBeAg/anti-HBe seroconversion, clearance of HBV DNA and normalization of ALT.	14/62 (22.5%)	26/60 (44%)	21/60 (35%)	NS

Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported	Not reported
% withdrawn due to adverse events	Not reported	Not reported	Not reported	Not reported

Follow up	Group 1: IFN-α for 6 months (n=62)	Group 2: IFN-α+ lamivudine for 6 months followed by lamivudine alone for 6 months (n=60)	Group 3: Lamivudine for 2 months then LAM plus IFN for 6 months, then lamivudine alone for 4 months (n=60)	p value
Log reduction of HBV DNA	Not reported	Not reported	Not reported	Not reported
Undetectable HBV DNA (6 months after end of treatment)	28/62 (45.7%)	53/60 (87.7%)	52/60 (87%)	Group 1 less than groups 2 or 3; group 2 and 3 NS
Undetectable HBV DNA (12 months after end of treatment)	38/62 (61.5%)	51/60 (85.7%)	43/60 (70.9%)	Not reported
Incidence of resistance	Not reported	Not reported	Not reported	Not reported
% with ALT normalisation (12 months after completion of therapy)	30/62 (48%) (month 18)	47/60 (79%) (month 24)	47/60 (78%) (month 24)	Group 1 less than groups 2 or 3 at 12 months after end of treatment; NS when Group 1 also reached month 24
HBeAg seroconversion (6 months after end of treatment)	18/62 (28.3%)	29/60 (49%)	21/60 (35%)	NS
HBeAg seroconversion (12 months after end of treatment)	20/62 (32.6%)	28/60 (46.9%)	21/60 (34.4%)	NS
HBeAg loss (6 months after completion of therapy)	22/62 (35%)	29/60 (49%)	25/60 (41.1%)	NS
HBeAg loss (12 months after completion of therapy)	29/62 (47%)	32/60 (53%)	21/60 (34.4%)	NS
Clearance of HBsAg and seroconversion of anti-HBs %	Not reported	Not reported	Not reported	NS
Sustained response 6 months after the end of therapy: HBeAg/anti-HBe seroconversion, clearance of HBV DNA and normalization of ALT.	18/62 (28.3%)	29/60 (49%)	21/60 (35%)	NS
Quality of life measures (EQ-5, SF-35, liver disease specific)	Not reported	Not reported	Not reported	Not reported

% withdrawn due to adverse events	Not reported	Not reported	Not reported	Not reported

Adverse effects:

Patients tolerated the treatment well. Therapy was not discontinued because of flu-like or gastrointestinal symptoms, which are the most common side-effects. Less common side-effects were myalgia, abdominal pain, fatigue, joint pain, weight loss and alopecia. These rare side-effects did not necessitate reducing the drug doses. No child developed severe neutropenia, thrombocytopenia or any other complication of bone marrow suppression.

Authors' conclusion:Although the ALT normalisation and HBV DNA clearance ratios of IFN plus LAM combination groups were better than the high dose IFN-α monotherapy group, no significant difference was found in the complete response ratios of all three groups.

Lamivudine + interferon simultaneously for 6 months, then continuing Lamivudine (until seroconversion + 6 months, or to 24 months for breakthrough or nonresponse) versus Lamivudine for 2 months, then add interferon for 6 months (lamivudine continued until seroconversion + 6 months, or to 24 months for breakthrough or nonresponse)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Kansu 2006	RCT-unclear blinding Multi-centre study in Turkey (11 centres)	N=177	Children with Chronic hepatitis B aged between 2 and 18 years Inclusion: Inclusion criteria: HBsAg positive; HBeAg positive; HBV DNA >5pg/mL for more than 6 months; ALT values more than 1.5 fold the normal upper limit (40 IU/L); HAI ≥5.	Group 1: Simultaneous group: lamivudine (3TC) (4 mg/kg/day, maximum 100 mg/day) plus IFN-α 2a	Group 2: Consecutive group: lamivudine (3TC) (4 mg/kg/day, maximum 100 mg/day) for 2	Up to a total of 24 months	ALT normalisation HBeAg seroconversion Clearance of HBV DNA Complete response at	Not reported

	No details of randomisation and allocation concealment.		Exclusion: Exclusion criteria: any contraindication to IFN-α 2a therapy; coninfection with HCV, hepatitis D virus or HIV, or any other liver disease; patients who had received IFN-α 2a within the year preceding the study. Baseline characteristics (see table below)	(9MU/m^2) thrice weekly, both for 6 months. Then 3TC continued until seroconversion + 6 months, or for 24 months for breakthrough or nonresponse (n=112). Total duration of treatment: 9-24 months Loss to follow up/reasons: not reported	months, then IFN-α 2a (9 MU/m^2) three times a week for 6 months. Then 3TC continued until seroconversion + 6 months, or for 24 months for breakthrough or nonresponse (n=65) Total treatment time 9-24 months Loss to follow up/reasons: not reported		the end of therapy: HBeAg/anti-HBe seroconversion, clearance of HBV DNA and normalization of ALT. Breakthrough serum HBV DNA >5pg/mL on two successive determinations after it had been undetectable, while still on treatment. Where available, YMDD mutations in patients with breakthrough. Relapse: reappearance of HBV DNA amd/or HBeAg after successful complete response	

Baseline characteristics

	Group 1 (n=112):	Group 2 (n=65):	p value
Mean±SD age	8.7 (3.5)	9.6 (3.8)	NS
Sex (% male)	68.7%	56.9%	NS
Naive (%)	67.8%	73.8%	NS
Mean ± SD serum ALT (IU/L)	134.2 (34.1)	147.0 (45.3)	NS
Mean (SD) HAI	7.4 (2.7)	7.1 (2.3)	NS
HBV DNA <200pg/mL	13.4%	15.4%	NS
HBV DNA 200-2000pg/mL	9.8%	18.5%	NS
HBV DNA >2000pg/mL	76.8%	66.2%	NS
Duration of treatment: 9-12 months 13-18	 24/112 (21.4%) 27/112	 9/65 (13.8%) 5/65 (7.7%)	

			months 19-24 months	(24.1%) 61/112 (54.4%)	51/65 (78.5%)				

There were no significant differences between the treatment groups for baseline characteristics.

Effect size

	Group 1 (n=112)	Group 2 (n=65)	p value
12 months:			
ALT normalisation n (%)	90 (80.4)	47 (72.3)	NS
Anti-HBe seroconversion n (%)	61 (54.5)	15 (23.4)	<0.01
Undetectable HBV DNA n (%)	100 (89.3)	55 (84.4)	NS
Breakthrough n (%)	3 (2.6)	2 (3.1)	NS
18 months:			
ALT normalisation n (%)	88 (78.8)	49 (75.8)	NS
Anti-HBe seroconversion n (%)	67 (60.2)	26 (39.4)	<0.05
Undetectable HBV DNA n (%)	90 (80.7)	45 (69.7)	NS
Breakthrough n (%)	10 (8.9)	9 (13.8)	NS
24 months:			
ALT normalisation n (%)	92 (82.2)	44 (68.2)	NS
Anti-HBe seroconversion n (%)	64 (57.3)	21 (31.8)	<0.05
Undetectable HBV DNA n (%)	84 (74.7)	39 (59.1)	NS
Breakthrough n (%)	6 (5.3)	5 (7.6)	NS
Complete response n (%)	62/112 (55.3%)	18/65 (27.6%)	<0.01
Anti HBs positive n (%)	11/112 (9.8%)	4/65 (6.2%)	NS
YMDD (n)	9	2	

Adverse effects: Flu-like syndrome was seen in all patients during the first 2-3 weeks of IFN-α 2a treatment. None of teh patients required dose reduction due to leucopenia or thrombocytopenia. No other adverse effect was observed.

Authors' conclusion: Simultaneous IFN-α 2a and 3TC yields a higher resxponse and earlier antiHBe seroconversion and viral clearance than consecutive combined therapy. Relapse rate is low. Predictors of response are high basal ALT and high HAI scores. 3TC can be administered for 24 months without any side effect and breakthrough rate is comparable with previous studies.

E.6.5 Cirrhosis and liver decompensation

E.6.5.1 Tenofovir (TDF) vs Tenofovir plus Emtricitabine (FTC) vs Entecavir (ETV)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Liaw 2011A	RCT – phase II Randomisation method: central, interactive voice response system.	N= 88	Mixed population (>60% HBeAg negative) with decompensated liver disease Inclusion: 18-69y, with HBV DNA >103 copies/ml or prior CTP score ≥7-12 (inclusive) or prior CTP score ≥7 and CTP ≤12 at screen, ALT <10 x ULN, calculated serum creatinine clearance ≥50 ml/min, Hemoglobin ≥7.5g/dl, total WBC count ≥1500/mm3, platelet count ≥30,000/mm3, alpha-fetoprotein ≤20ng/ml, and no	Group 1 Tenofovir (300mg/day) (n=32) Total duration of treatment:	Group 2 Tenofovir (300mg/day) + Emtricitabine (FTC) (200mg/day)	48 weeks treatment No F/U	% of patients with undetectable HBV DNA (<400 copies/mL) log reduction in HBV DNA	Not stated

	Randomisation was stratified by CTP score and prior lamivudine use Blinding: Partially double blind (see Notes section) Allocation concealment: adequate A noncompleter / switch = failure analysis was performed. Patients who stopped the study or switched to open-label FTC/TDF were considered as failures for categorical endpoints.		evidence of HCC Setting: International multicentre trial (39 sites incl. Europe, Canada, Singapore, Taiwan, the US) Exclusion: Coinfected with HCV or HDV or HIV, prior TDF or ETV use, ADV exposure ≥24 months, current grade 2 or higher hepatic encephalopathy, history (within 60 days) of variceal bleeding, hepatorenal syndrome, Grade 3 or 4 hepatic encephalopathy, or spontaneous bacterial peritonitis, solid organ or bone marrow transplant, or use of hepatotoxic or nephrotoxic drugs including those affecting renal tubular secretion Baseline characteristics TDF (n=45) / TDF + FTC (n=45) / ETV (n=22) Median age (years): 52 / 50 / 54 Male, n (%): 37 (82.2) / 40 (88.9) / 17 (77. Race, n (%) Asian: 23 (51.1) / 24 (53.3) / 13 (59. White: 19 (42.2) / 20 (44.4) / 8 (36.4 other: 3 (6.7) / 1 (2.2) / 1 (4.5) Median HBV DNA (log10 copies/ml) (Q1, Q3): 5.7 (4.9, 6.6) / 6.28 4.5, 7.3) / 5.93 (4.2, 7. Median ALT (I/U) (Q1, Q3): 48 (31, 73) / 54 (34, 98) / 52 (41, 66 HBeAg negative, n (%): 31 (68.9) / 27 (60) / 15 (68.	48 weeks 32/45 completed 48 weeks double-blind treatment; 5/45 switched to open label Emtricitabine plus tenofovir prior to week 48 and completed treatment. 8/45 discontinued double-blind drug prematurely	(n=40) 40/45 completed 48 weeks double-blind treatment; 2/45 switched to open label Emtricitabine plus tenofovir prior to week 48 and completed treatment. 3/45 discontinued double-blind drug prematurely Total duration of treatment: 48 weeks Group 3 Entecavir (0.5 or 1 mg/day)		Child-Pugh score ≥2 points decrease Model for end stage liver disease score (MELD) Resistance Mortality Ascites Hepatic encephalopathy Hepatocellular carcinoma	

Median Child-Turcotte-Pugh score (Q1, Q3)	7 (6,8)	7 (6,9)	7 (6,8)		(n=16) Total duration of treatment: 48 weeks 16/22 completed 48 weeks double-blind treatment; 3/22 switched to open label Emtricitabine plus tenofovir prior to week 48 and completed treatment. 3/22 discontinued double-blind drug prematurely			
Median Model for end stage liver disease score (Q1,Q3)	11 (9,14)	13 (10,17)	10.5 (9					
Previous CHB treatment, n (%) Lamivudine ≥6 months Adefovir	19 (42.2) 9 (20)	17 (37.8) 10 (22.2)	8 (36.4 5 (22.7					
HBV genotype, n (%) A B C D E F G	8 (17.8) 9 (20) 10(22.2) 15 (33.3) 1 (2.2) 0 0	8 (17.8) 13 (28.9) 11 (24.4) 10 (22.2) 0 1(2.2) 1(2.2)	4 (18.2 6 (27.3 5 (22.7 4 (18.2 0 1 (4.5) 0					

Effect size

At end of treatment (week 48)	TDF (n=32)	TDF + FTC (n=40)	ETV (n=16)
Median (IQR) change from baseline in HBV DNA (log10 copies/mL)	-3.11 (-4.1, -2.4)	3.92 (-5.2, -2.2)	-3.4 (-5, -1.3)
Log reduction in HBV DNA log copies /mL (SD)	3.30 (1.516)	3.72 (1.769)	3.24 (1.919)
Undetectable HBV DNA (<400 copies/mL), n/N (%)	23/32 (70.5)	35/40 (87.8)	12/16 (72.7)
ALT normalisation, n/N (%)	12/26 (46.2)	16/25 (64)	7/16
CTP score ≥2 points decrease, n/N (%)	7/27 (25.9)	12/25 (48)	5/12 (41.7)
Median (IQR) change from baseline in MELD score	-2.0 (-12,3)	-2.0 (-18, 4)	-2.0 (-10,1)
HBeAg loss, n/N %)	3/14 (21.4)	4/15 (26.7)	0/7
HBeAg seroconversion, n/N (%)	3/14 (21.4)	2/15 (13.3)	0
Mortality, n (%)	2 (4.4)	2 (4.4)	2 (9.1)
Resistance	0	0	0
Clinical adverse events Ascites Hepatic encephalopathy	 4 3	 2 1	 4 1
Liver transplantation	2	4	0
Incidence of hepatocellular carcinoma	3	1	1
Discontinued study drug due to adverse events, n	6		

Authors' conclusion:. All treatments were well tolerated in patients with decompensated liver disease due to CHB with improvement in virologic, biochemical and clinical parameters. No patient was found to develop resistance to any study drug.

Notes: Because the trial enrolled patients with decompensated liver disease, patients with a <2 log10 copies/mL decrease in HBV DNA at week8 (and greater than baseline value) could initiate open-label FTC/TDF fixed dose combination and continue in the study, or remain on blinded therapy. Patients with a virologic breakthrough (≥1 log10 copies/mL increase from nadir on two consecutive determinations or consecutive HBV DNA ≥400 copes/mL after being <400 copies/mL) or who had plasma HBV DNA levels remaining >400 copies/mL (confirmed) at or after 24 weeks of treatment could also switch to open-label FTC/TDF and continue in the study, or remain on blinded therapy.

This analysis evaluated the comparative safety of two TDF-containing regimens and ETV through 48 weeks. The study was not designed to detect differences in efficacy among the three treatment regimens.

E.6.5.2 Entecavir (ETV) vs Adefovir (ADV)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Liaw 2011	RCT Randomisation method: Unclear Not blocked or stratified Blinding: Open-label Allocation concealment: unclear	N= 133	Mixed CHB patients with hepatic decompensation (CTP score ≥7), ~50% HBeAg (+) and (-); experienced or naïve for treatment with nucleos(t)ide analogues Inclusion: subjects with CHB (detectable HBsAg for ≥6 months) who had liver decompensation (CTP≥7), aged ≥16y, without coinfection of HCV, HDV, HIV or other known liver disease. HBV DNA ≥105 copies/mL, ALT ≤15xULN, serum creatinine ≤2.5 mg/dL, alpha-fetoprotein <400ng/mL, and no liver mass consistent with HCC on imaging performed within 4 weeks prior to randomisation. Setting: multicentre international trial (52 sites)	Entecavir (1mg/day) (n=71) Total duration of treatment: 96 weeks Lost to follow up/ reasons (overall):consent withdrawn, n=6; death, n=3; AE, n=1;	Adefovir (10mg/day) (n=62) Total duration of treatment: 96 weeks	No F/U	Assessed at week 48: % of patients with undetectable HBV DNA (<300 copies/mL) log reduction in HBV DNA Child-Pugh score ≥ 2 points	Bristol-Myers Squibb Pharmaceutical Research Institute

			Exclusion: previously treated with ETV, ADV or tenofovir Baseline characteristics	lost to follow up, n=1, administrative reason, n=1; other, n=11			decrease Mean change in Model for end stage liver disease score (MELD) Incidence of hepatocellular carcinoma (HCC) Liver transplantation Resistance Mortality	

	ETV (n=71)	ADV (n=62)
Mean age, years (SE)	51 (1.2)	53 (1.1)
Male, n (%)	78 (78)	64 (70)
Race, n (%) Asian White Black/African	 55 (55) 35 (55) 5 (5)	 49 (54) 28 (31) 5(5)
Mean HBV DNA (log10 copies/ml) (SE)	7.53 (0.18)	8.16 (0.23)
Mean ALT (U/L) (SE)	99.2 (11.1)	100 (8.6)
HBeAg positive, n (%)	54 (54)	50 (55)
Mean Child-Turcotte-Pugh score (SE)	8.81 (0.20)	8.35 (0.19)
CTP class, n (%) A B C	 7 (7) 63 (63) 30 (30)	 10 (11) 61 (67) 20 (22)
Mean Model for	17.1 (0.50)	15.3 (0.48)

			end stage liver disease score (SE)							
			Previous Lamivudine treatment, n (%)	39 (39)	34 (37)					
			Lamivudine resistant, n (%)	36 (36)	30 (33)					

Effect size

Outcomes assessed at week 48	ETV (n=71)	ADV (n=62)
% patients with log reduction of HBV DNA (log10 copies/mL)	-4.48 (N=69)	-3.40 (N=61)
Subgroup analysis, mean (SE)*		
HBeAg (+)	(N=34)	(N=31)
	-5.07 (0.319)	-4.21 (0.528)
HBeAg (-)	(N=35)	(N=30)
	-4.27 (0.241)	-3.58 (0.467)
Undetectable HBV DNA (<300 copies/mL), n/N (%)		
Overall	57/71	18/62
Subgroup analysis*		
HBeAg (+)	25/54 (46)	9/51 (18)
HBeAg (-)	32/46 (70)	9/40 (23)
ALT normalisation, n/N (%)	49/71 (69)	33/62 (53)
CTP score ≥2 points decrease, n/N (%)	35/71 (49)	25/62 (40)

Mean change from baseline in MELD score (SE)*	-2.6 (0.62)	-1.7 (0.5)
HBeAg loss, n/N (%)**	6/54 (11)	9/51 (18)
HBeAg seroconversion, n/N (%)**	3/54 (6)	5/51 (10)
HBsAg loss, n/N (%)	5/71 (7)	0/62 (0)
Incidence of HCC, n/N (%)	12/71 (17)	18/62 (29)
Mortality, n (%)	23/71 (32)	29/62 (47)
Liver transplantation, n (%)	11/71 (16)	3/62 (5)
Resistance, n (%)	0/71 (0)	0/62 (0)
Discontinued study drug due to adverse events, n/N (%)	7/71 (10)	5/62 (8)

*ITT analysis

**Analysis limited to HBeAg positive patients at baseline (ETV, n =54; ADV, n=51).

Authors' conclusion:. ETV demonstrated superior virologic efficacy to ADV in a population of patients with CHB who had hepatic decompensation. Biochemical and clinical benefits were also demonstrated. ETV was well tolerated, and early mortality rates were consistent with rates observed in similar populations treated with LAM.

Notes:

E.6.5.3 Telbivudine vs lamivudine

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chan 2012	RCT	N=232	Treatment-naive patients with decompensated cirrhosis owing to chronic hepatitis B infection	600mg telbivudine	100mg lamivudine	52 and 104	Primary: proportion of	Novartis Pharma,

	Double blind 80 medical academic centres in 21 countries Central randomisation, stratified by screening CTP score (≥9 or <9) and ALT (normal or >1 x ULN) 120 patients per group provided power of 90% at one-sided p=0.05 to detect noninferiority (margin -10%) between treatments		Inclusion: Age 18-70 years; decompensated CHN (clinical history, Child- Turcotte- Pugh score ≥7, cirrhosis or portal hypertension), serum HBV DNA ≥5 log $_{10}$ copies/mL, not pregnant or breastfeeding, not coinfected with hepatitis C or D or HIV. Exclusion: ever treated with lamivudine, adefovir or any investigational anti-HBV nucleoside/nucleotide analogue, or who had received interferon or other immunomodulatory treatment within previous 12 months Baseline characteristics: Telbivudine (n=114) / Lamivudine (n=114) Mean (SD) age years: 49.6 (10.9) / 51.9 (10.0) Gender n(%) male: 87 (76.3) / 81 (71.1) Asian: 74 (64.9) / 74 (64.9) Middle Eastern/Indian subcontinent: 28 (24.6) / 21 (18.4) Caucasian: 10 (8.8) / 17 (14.9) Other: 2 (1.8) / 2 (1.8) HBeAg negative n (%): 63 (55.3) / 68 (59.6) HBV DNA mean (SD) log $_{10}$ copies/mL: 7.6 (1.9) / 7.6 (1.9)	daily for 104 weeks (n=116) week 52: 114 in ITT population (1 discontinued prior to receiving any drugs and 1 no HBV DNA measurements after baseline)	daily for 104 weeks (n=116) Week 52: 114 in ITT population (2 no HBV DNA measurements after baseline)	weeks (on treatment)	patients with HBV DNA <10,000 copies/mL (Iter modified to <300 copies/mL), normal ALT and Child-Turcotte-Pugh score improvement/ stabilisation at week 52. Secondary: Undetectable HBV DNA by PCR (<300 copies/mL [lower limit of detection])' ALT normalisation; virological breakthrough; time to virological breakthrough; rate of genotypic resistance; patient survival; adverse events	AG

	on clinical response (estimated rates 40% for lamivudine and 60% for telbivudine) adjusted for 25% drop out Intention to treat analysis		<table><tr><td>Mean (SD) ALT IU/mL</td><td>75.1 (54.4)</td><td>84 (87.8)</td></tr><tr><td>Mean (SD) CTP score</td><td>8.1 (1.6)</td><td>8.5 (1.8)</td></tr><tr><td>Genotype A B C D Other</td><td> 6 (5.3) 26 (22.8) 48 (42.1) 33 (28.9) 1 (0.9)</td><td> 11 (10) 15 (13.2) 58 (50.9) 29 (25.4) 1 (0.9)</td></tr></table>				

Effect size

	52 weeks			104 weeks		
	Telbivudine (n=114)	Lamivudine (n=114)	Comparison	Telbivudine (n=114)	Lamivudine (n=114)	Comparison
HBV DNA <10,000 copies/mL n (%)	85 (74.6)	82 (71.9)	p=0.69	65 (57.0)	55 (48.2)	p=0.20
Undetectable HBV DNA <300 copies/mL n (%)	74 (64.9)	70 (61.4)	p=0.62	56 (49.1)	45 (39.5)	p=0.15
ALT normalisation n (%) of those with raised ALT at baseline	54/83 (65.1)	57/84 (67.9)	p=0.73	51/83 (61.4)	44/84 (52.4)	p=0.25
CTP score	36 (31.6)	44 (38.6)	p=0.28	44 (38.6)	46 (40.4)	p=0.83

improvement (decrease ≥2 points)						
Virological breakthrough (%)				28% (denominator unclear)	39% (denominator unclear)	not stated
Genotypic resistance n (%)	13 (11)	16 (14)	not stated	Additional 12/69 (17.4)	Additional 17/68 (25)	not stated
Genotypic resistance n (%) in non-responders at week 52/104 respectively	11/37	13/42	p=0.91	10/45	17/56	p=0.36
HBeAg seroconversion (of those HBeAg positive at baseline) n (%)	13/51	11/45		14/51	16/45	not stated
Survival Died	109/116 7/116	106/116 10/116	not stated	104/116 12/116	99/116 17/116	p=0.16

Authors' conclusion: In patients with difficult-to-treat HBV-related decompensated cirrhosis, telbivudine was safe ans well tolerated. Telbivudine for 104 weeks compared to lamivudine was associated with a higher rate of patients with both viral suppression and ALT normalisation, a trend towards higher rate of survival and significant improvement in glomerular filtration.

E.6.6 Prophylactic treatment

Reference	Study type	Number of	Patient characteristics	Intervention	Comparison	Length of follow-	Outcome measures	Source of

		patients				up		funding
Long 2011	RCT Single centre No details given about randomisation procedure or allocation concealment.	42	Inclusion: HBsAg positive breast cancer patients during chemotherapy who were able to visit the clinic at least every 21 days during the study. Exclusion: Decompensated liver disease at screening; those who had been treated with chronic antiviral therapy known to have activity against HBV within the previous 6 months; those who had acute fulminant hepatitis; those who were recipients of any investigational new drug within 30 days of the first dose of the study drug; and those who were pregnant, lactating or had pancreatitis. Baseline characteristics Prophylactic LAM (n=21) / No prophylact LAM (n=21) No. of females (%): 21 (100) / 21 (100) Median age: 45(29-64) / 43(20-62) Stage I: 10 / 4 II: 8 / 14 III: 2 / 1 IV: 1 / 2 HBsAb Negative: 19 / 20 positive: 2 / 1 HBeAg Negative: 19 / 18	Prophylactic lamivudine, 100mg/day for 7 days prior to start of chemotherapy . Treatment was then continued throughout the course of chemotherapy and until 8 weeks after its discontinuation. (n=21)	No prophylactic lamivudine Patients received lamivudine only after proven HBV reactivation during chemotherapy. Treatment was continued for 8 week after the discontinuation of chemotherapy (n=21)	8 weeks after the completion of chemotherapy	HBV reactivation Increase in HBV DNA >10 fold when compared to baseline or an absolute increase of >1x109 copies/mL in the absence of any other systemic infection Hepatitis 3 x ULN (58IU/L) or an absolute increase of ALT to more than 100IU/L when compared to the baseline pre-chemotherapy value. Mortality	Not stated

Positive	2	3
HBeAb Negative positive	 3 18	 4 17
HBcAg Negative Positive	 14 2	 13 3
HBcAb Negative Positive	 0 21	 1 20
HB-PreS1-Ag status Negative Positive	 13 8	 15 6
Median HBV DNA (copies/mL)	6.16x106	3.99 x 106
Median ALT (U/L)	22.3 (7-96)	14.6 (6-27)
Median total bilirubin (µmol/l)	13.6(5.6-21.6)	16.7(6.4-44.1)
Liver ultrasonography Normal Fatty liver	 1 5 3	 19 1
Chemotherapy regimen Anthracycline +	10	16

			taxane based Taxane based Anthracycline based Type of chemo Adjuvant Neoadjuvant Adjuvant + neoadjuvant salvage No significant baseline differences between groups.	 7 2 17 2 1 1	 4 1 14 4 1 2				

Effect size

	Prophylactic lamivudine N=21	No prophylactic lamivudine N=21
Occurrence of HBV reactivation (%)	0(0)	6(28.6)
Occurrence of hepatitis (%)	5(23.8)	3(14.3)
Hepatitis due to HBV reactivation (%)	0(0)	0(0)
Overall mortality (%) Mortality due to HBV reactivation (%)	0(0) 0(0)	1(4.8) 0(0)

The median number of chemotherapy cycles was 6 (range 1-8) in the control group.
The median number of chemotherapy cycles was 6 (4-8) in the prophylactic group.

The antiviral agent was well tolerated and was not associated with any unexpected effects or additional toxicity.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hsu 2008	RCT Multicentre, Taiwan Randomised 1:1 Randomisation list by permuted block randomisation. The randomisation code was given only when the patient passed the eligibility check. Sample size	51	Inclusion: HBV carriers (HBsAg positive) with newly diagnosed histologically proven intermediate grade or high grade non-hodgkin's lymphoma who underwent chemotherapy. Age 16-75y; ALT<5xULN, bilirubin <2.5mg/dl, Eastern Cooperative Oncology group performance score 0-2 Exclusion: Child pugh class B or C cirrhosis, grade 2 or greater heart failure by the New York Heat Association classification, previous chemotherapy or radiotherapy, concurrent glucocorticoid therapy for other reasons, or other primary liver diseases, such as HCV, HDV/HIV or Wilson's Disease. Chemotherapy regimen – CHOP regimen. The treatment cycles were repeated every 21 days. Patients who achieved a complete response were given 2 more cycles of chemotherapy, for a min. of 6 cycles. Baseline characteristics Prophylactic lamivudine | Therapeutic lamivudine	Prophylactic lamivudine (100mg/day) Patients started LAM from day 1 of the 1st course of chemotherapy and continued treatment until 2 months after completion of chemotherapy. If 2nd line chemotherapy was used, LAM at the same dosage was continued	Therapeutic lamivudine Patients received chemo alone and started LAM only if ALT elevated to >1.5 fold ULN during F/U and continued LAM treatment until hepatitis was resolved. (n=25) 13 completed assigned therapy and observation.	12 months of ending chemotherapy	1. HBV reactivation during the 12 months after starting chemotherapy 2. Heptatitis flare >3 fold increase of ALT (>100IU/L) 3.Resistance	Not stated

	calculation given				until 2mo after completion of 2nd line chemotherapy. (n=26) 21 completed assigned therapy and observation.				

	(n=26)	(n=25)
Median age, range	50.5 (32-67)	41 (20-74)
M/F	12/14	13/12
HBeAg* Negative Positive	 24 2	 17 8
HBV DNA (copies/mL)* <1,000,000 >1,000,000	 23 3	 16 9
HBV genotype B B+C C	 18 1 0	 15 0 2

*baseline differences between groups, p=≤0.05

Effect size

The patients received a median of 6 cycles of chemotherapy (range1-8 cycles).
The median duration of LAM treatment was 190 days (range85-385) for the prophylactic group and 139 days (range17-276) for the therapeutic group.
HBV reactivation rate was 30.8% (95%CI=14.3-51.8%) in the prophylactic group and 60% (95%CI=38.7-78.9%) in the therapeutic group (p=0.05).
Patients in the prophylactic group had a significantly longer time to HBV reactivation (HR=0.35, 95%CI=0.15-0.84;p=.02)

During protocol treatment	Prophylactic LAM (n=21)	Therapeutic LAM (n=13)
HBV reactivation *	3	14
Hepatitis flare*	4	15
HBV reactivation and hepatitis flare*	2	12
Hepatitis related mortality	0	0

After protocol treatment	(n=21)	(n=13)
HBV reactivation	5	3
Hepatitis flare	7	3
HBV reactivation and hepatitis flare	4	1
Hepatitis related mortality	2	0
Resistance	2	0

*p=0.001

The incidence of HBV reactivation and hepatitis flare did not differ between the two groups after protocol treatment.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lau 2003	RCT Randomised 1:1 Sealed envelopes Hong Kong Clinical data were collected and monitored by GSK.	30 consecutive patients	Inclusion: HBsAg positive lymphoma adult patients undergoing intensive chemotherapy Exclusion: ALT >10xULN at screening. Decompensated liver disease. Previous antiviral treatment over the last 6 months. Baseline characteristics Prophylactic lamivudine (n=15): Median age, range 50.6 (23-98); Male (%) 8(53); Non-Hodgkin 12; Hodgkin 3 Pre-emptive lamivudine (n=15): Median age, range 51.2 (24-98); Male (%) 9(60); Non-Hodgkin 12; Hodgkin 3	Prophylactic lamivudine (100mg/day) 1 week before chemotherapy and continued for at least 6 weeks after the completion of the last course of chemotherapy (n=15)	Pre-emptive lamivudine Patient received LAM if there was serological evidence of HBV reactivation (serial 2wk interval HBV DNA monitoring), and continued for at least 6	12 weeks after withdrawnal from LAM	1.Hepatitis >3fold increase of ALT on 2 consecutive occasions at least 5 days apart 2.Hepatitis due to HBV reactivation Preceded or accompanied by an increase of HBV DNA to >10 times compared to	Supported partly by Glaxosmithkline

	ITT Sample size calculation given No info on loss to follow up		Pre chemo HBV serology HBeAg positive HBV DNA positive HBV DNA (pg/ml), median (range) HBV genotype B C No sig. baseline differences	 4(27) 3(20) 0(0-490) 4(27) 11(73)	 4(27) 5(33) 0(0-2248) 7(47) 8(53)		weeks after the completion of the lsat course of chemotherapy (n=15)		baseline and HBV DNA turned from negative to positive 3.All-cause mortality 4.Mortality due to hepatitis	

Duration of prophylactic treatment: median of 32 (8-57) weeks
Duration of pre-emptive treatment: median of 15 (13-32) weeks

Median onset of HBV reactivation after chemotherapy is 16 (1-36) weeks (for both groups).
Median onset of hepatitis after chemotherapy is 14 (11-15) weeks in the prophylactic group and 15 (5-36) weeks in the pre-emptive group.

Effect size – after chemotherapy

	Prophylactic LAM (n=15)	Pre-emptive LAM (n=15)
Hepatitis Hepatic failure Hepatitis related to HBV reactivation	3 0 0	10 1 7
HBV reactivation*	0	8
Overall mortality Hepatitis B related mortality	0 0	1 0

*p=0.002

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Li 2006	Non-randomised trial + use of historical controls China Sample size calculation given	156	Inclusion: HBsAg positive patients with lymphoma (histologically confirmed); HBsAg positive, HBcAb, HBeAg, HBeAb positive, normal LFTs, no HAV, HCV, HDV or HEV infections; no liver involvement of lymphoma or other diseases; and to have received ≥4 cycles of chemotherapy for no incidence of hepatitis. Exclusion: -- Baseline characteristics Male (%): Prophylactic Lamivudine (n=40) 72 (62.1); No prophylactic lamivudine (n=116) 25(62.5) Median age (range): 41(12-75); 40(16-74) Non-hodgkin: 111(95.7); 36(90) Hodgkin: 5(4.3); 4(10) HBeAg positive	Prophylactic lamivudine (100mg/day) 7 days before and until at least 8 weeks after they discontinued chemotherapy (n=40)	No prophylactic Patients who received chemotherapy without lamivudine (n=116)	12 weeks after completion of chemotherapy	Hepatitis An increase ≥3 fold in ALT (>1.25xULN of 50IU/L) or an absolute increase of ALT >100IU/L compared to baseline Hepatitis due to HBV reactivation An increase in HBV DNA >10fold compared with baseline or an absolute increase >105	Not stated

								copies/mL in the absence of systemic infection Resistance	

	47(40.5)	23(57.5)
Use of anthracyclines	111(95.7)	35(87.5)
Use of steroids	107(92.2)	37(92.5)

No significant baseline differences between the two groups. However, HBV DNA was not measured in the control group.

Effect size

The median number of chemotherapy cycles was 6 (4-13)
The median duration of LAM therapy was 12 weeks after the completion of chemotherapy (range, 8-64 weeks)

	Prophylactic LAM N=40	No prophylactic n=116
All- cause hepatitis*	7(17.5)	60(51.7)
Severity of hepatitis* Grade 1 2 3 4	 4(3.4) 14(12.1) 15(12.9) 27(23.3)	 4(10) 2(5) 1(2.5) 0
Hepatitis attributed to HBV reactivation	1(2.5)	
Mortality during treatment	0	6(5.2)
Resistance	1	0

*p=0.000

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Li 2011</td><td>Non-randomised controlled trial (use of historical controls)

Multicentre

China</td><td>123</td><td>Inclusion: malignant lymphoma patients (confirmed by histology) during chemotherapy; age ≥16years; HBsAg positive, HBeAb, HBeAg or HBcAb positive by serology. No prior anti-HBV treatment; normal liver function with ALT, AST, total bilirubin, alkaline phosphatise, GGT ≤1.25xULN and albumin ≥30g/L; no evidence of coinfection with HAV, HEV, HCV, HDV or HIV.

Exclusion: as above.

Baseline characteristics
<table>
<tr><th></th><th>Prophylactic ETV (n=34)</th><th>Prophylact LAM (n=89)</th></tr>
<tr><td>N male (%)</td><td>22 (64.7)</td><td>52 (58.4)</td></tr>
<tr><td>Median age (range)</td><td>44 (17-74)</td><td>46 (20-81)</td></tr>
<tr><td>Hodgkin’s disease
B-cell non-hodgkin
T cell non-hodgkin</td><td>1 (2.9)

29 (85.3)

4 (11.8)</td><td>4 (4.5)

77 (86.5)

8 (9)</td></tr>
<tr><td>Hepatic cirrhosis</td><td>1 (2.9)</td><td>3 (3.3)</td></tr>
</table></td><td>Prophylactic entecavir 0.5mg/day (n=34)

Both drugs administered 7 days before chemotherapy and ending 6 months after completion of chemotherapy.</td><td>Prophylactic lamivudine 100mg/day (n=89)</td><td>During and after 6 months of chemotherapy

No drop out in both groups</td><td>1.HBV reactivation
- an increase in HBV DNA levels ≥10 fold or an absolute increase ≥105 copies/mL when compared with baseline value

2.Hepatitis
- ≥3 fold increase in ALT >58IU/L or as an absolute increase in ALT to >100U/L compared with baseline level</td><td>Guangdong and Guangzhou Committee of Science and Technology, People’s Republic of China</td></tr>
</table>

HBsAg positive	32 (94.1)	86 (96.6)
HBeAg positive	12 (35.3)	27 (30.3)
HBcAb positive	32 (94.1)	89 (100)
HBV DNA >105 copies/mL	11 (32.4)	31 (34.8)
Median HBV DNA, range (copies/mL)	1.96 x 104 (0-3.32x108)	1.73 x 104 (0-3.85 x 109)
Use of steroids	34 (100)	89 (100)
Use of rituximab	24 (70.6)	58 (65.2)
Hematopoietic stem cell transplantation	3 (8.8)	11 (12.4)

3.HBV-related hepatitis
-HBV reactivation preceding or accompanying hepatitis during and after 6 months of chemotherapy, in the absence of clinical or laboratory features of acute infection with other hepatitis viruses or systemic disease.

4.Mortality

Both groups received 8 cycles of CHOP regimen.

Effect size

	Prophylactic Entecavir n=34	Prophylactic Lamivudine n=89
Incidence of hepatitis	2 (5.9)	24 (27)

Severity of hepatitis Grade I II III IV	 1 (2.9) 0 1(2.9) 0	 5 (5.6) 6 (6.7) 9 (10.1) 4 (4.5)
HBV reactivation	4 (11.8)	18 (20.2)
HBV related hepatitis	0	11 (12.4)
Severe hepatic failure	0	1 (1.1)
Mortality due to hepatic failure	0	1 (1.1)
Resistance	0	1 (1.1)

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yeo 2004A	Non-randomised trial + use of historical controls Hong Kong Sample size	258	Inclusion: HBsAg positive cancer patients undergoing cytotoxic chemotherapy who were able to attend clinic at least every 10 days during the study. Exclusion: hepatocellular carcinoma or head and neck cancers, decompensated liver disease at screening, those who had treated with chronic viral therapy known to have activity against HBV within the previous 6 months, those who had acute fulminant hepatitis, those who were recipient of any investigational new drug within	Prophylactic lamivudine 100mg/day (n=65) Started within 7 days before start of chemotherapy. For patients with renal insufficiency, the	No prophylactic lamivudine (n=193)	8 weeks after completiong of chemotherapy	1.Hepatitis -≥3 fold increase in ALT that exceeded the upper limit of normal (<58IU/L) or an absolute increase of ALT to >100U/L) when compared with	GlaxoWellcome

	calculation was given by study		30 days of the first dose of study drug, and those who were pregnant, lactating or had pancreatitis. Baseline characteristics Prophylactic LAM (n=65) / No prophylactic LAM (n=193) N male (%): 34 (52.3) / 82 (42.5) Median age (range): 49 (35.77) / 49 (20-78) Tumour types Non-hodgkin: 17 (26.2) / 28 (14.5) Breast cancers: 19 (29.2) / 62 (32.1) GI cancers Lung cancers: 18 (27.7) / 49(25.4) Gynecologic malignancies: 4(6.2) / 9(4.7) Other cancers: 4 (6.2) / 21(10.9) 3 (4.6) / 26 (12.4) Median ALT, range (IU/L): 30 (13-430) / 28(10-234) Median total bilirubin, range (µmol/l): 6(2-22) / 7(1-38) Median HBV DNA, range (x106 ge/ml): <0.7 (<0.7-2760) / <0.7(<0.7->4500) HBeAg positive: 7(10.8) / 31 (61.1) No. with detectable HBV: 13(20) / 37 (19.2)	daily LAM dose was adjusted according to creatinine clearance. Treatment was then continued throughout the course of chemotherapy for 8 weeks after stopping chemotherapy.			baseline pre-chemotherapy value 2.Hepatitis attributable to HBV reactivation -an increase in HBV DNA of 10 fold when baseline with baseline or an absolute increase of >1000x106 ge/ml, in the absence of other systemic infection 3.All-cause mortality 4.Mortality due to HBV reactivation 5.Mortality due to progressive malignant disease	

DNA		
Use of steroids during chemotherapy	37 (56.9)	90 (46.6)

Median duration of chemotherapy:
Prophylactic LAM = 6 (1-10) cycles
No treatment = 5 (1-13) cycles

Median duration of prophylactic LAM = 161 (56-367) days.

Effect size

N (%)	Prophylactic LAM (n=65)	No prophylactic LAM (n=193)
Incidence of hepatitis*	11 (17.5)	86 (44.6)
Hepatitis due to HBV reactivation*	3 (4.6)	47 (24.4)
Severity of hepatitis*		
Mild (ALT≤2xULN)	5 (7.9)	22 (11.4)
Cases due to HBV reactivation	2	9
Moderate (ALT>2-≤5xULN)	3 (4.8)	28 (14.5)
Cases due to HBV reactivation	1	13
Severe (>5xULN)	3 (4.8)	36 (18.7)
Cases due to HBV reactivation	0	25
Overall mortality	5 (7.7)	23 (11.9)
Causes		
HBV reactivation	0	5 (2.6)
Progressive malignant disease	5(7.7)	17 (8.8)

*P<0.05

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yeo 2005	Non-randomised trial + use of historical controls	37	Inclusion: HBsAg positive nasopharyngeal cancer patients who were able to attend clinic at least every 10 days during the study. Exclusion: hepatocellular carcinoma or head and neck cancers, decompensated liver disease at screening, those who had treated with chronic viral therapy known to have activity against HBV within the previous 6 months, those who had acute fulminant hepatitis, those who were recipient of any investigational new drug within 30 days of the first dose of study drug, and those who were pregnant, lactating or had pancreatitis. Baseline characteristics Prophylactic LAM (n=16) / No prophylact LAM (n=21 Median age, (range): 46.5 (30-58) / 46 (40-65) M/F: 14/2 / 15/6 HBeAg positive: 1 (6.7) / 4 (19.1) Median ALT, : 44.5 (19-96) / 29 (12-84)	Prophylactic lamivudine (n=16) Drug was administered prior to and until 8 weeks after stopping chemotherapy.	No prophylactic lamivudine (n=21)	8 weeks after completion of chemotherapy	1.Hepatitis -≥3 fold increase in ALT that exceeded the upper limit of normal (<58IU/L) or an absolute increase of ALT to >100U/L) when compared with baseline pre-chemotherapy value 2.Hepatitis attributable to HBV reactivation -an increase in HBV DNA of 10 fold when baseline with baseline or an absolute increase of >1000x106 ge/ml, in the absence of	GlaxoWellcome

			IU/L (range)						other systemic infection	
			Median total bilirubin, µmol/l (range)	8 (3-45)	6 (3-20)					
			Presence of liver metastasis	3 (18.8)	2 (9.6)				3.Mortality due to HBV reactivation	
			Use of corticosteroids	7 (43.8)	7 (33.3)					

Effect size

Median number of chemotherapy cycles was 5 (range 1-6) cycles in the control group.
Median number of chemotherapy cycles was 6 (range 4-10) cycles in the prophylactic group.
Mean duration of lamivudine therapy was 146 days (78-323 days).

	Prophylactic lamivudine n=16	No prophylactic n=21
Incidence of hepatitis*	1 (6.3)	7 (33.3)
Hepatitis attributable to HBV reactivation*	0	6 (28.6)
Severity of hepatitis* Mild or moderate (≤5xULN) Severe (ALT >5xULN)	 1 (6.3) 0	 2 (9.6) 5 (23.8)
Mortality due to HBV reactivation	0	1 (4.8)

*P<0.05.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Jang 2006	Prospective single centre randomised open label trial Korea 1:1 randomisation via computer generated allocation Sample size calculation given by study	76	Inclusion: patients with HBV related unresectable hepatocellular carcinoma (confirmed by histology or elevated serum alpha fetoprotein >400ng/ml with typical radiology findings) undergoing transarterial chemo-lipiodolisation (TACL) No patients received glucocorticoid therapy. Exclusion: previous history of antiviral therapy; baseline ALT 2.5xULN; HBV DNA >107 copies/ml; extrahepatic metastasis; main portal vein thrombosis; underlying cardiac or renal diseases; coinfection with HCV or HIV; Child Pugh classification B or C; or preexisting evidence of hepatic decompensation. Baseline characteristics {table1}	Preemptive lamivudine 100mg/day, from the start of TACL and continued for 12 months after the completion of TACL (n=36) Lost to F/U: 1 Not received TACL: 1	Control group (n=37) For patients in control group who developed hepatitis due to HBV reactivation, LAM was started immediately. Lost to F/U: 1	Median follow up of 5.8 months	1.HBV reactivation ->10 fold increase in HBV DNA compared with baseline level 2.Hepatitis 3.Hepatitis attributable to HBV reactivation -≥3 fold increase in ALT to a level that exceeded 100IU/L (reference range 33IU/L) in patients with HBV reactivation in the absence of clinical feature s of tumour progression, hepatotoxic drugs, treatment-related hepatic damage or other systemic	Not stated

{table1}

	Preemptive lamivudine N=36	Control N=37
M:F	30:6	31:6
Age, mean (SD)	52.5(8.4)	53.2(9)
HBeAg positive	9	8

			HBV DNA (x103 copies/mL), median (range)	146.5 (<2-9345)	139.2(<2-879			infections. 4.Hepatic decompensation -newly developed encephalopathy, ascites, variceal bleeding, bilirubin more than 2.5xULN, or prolongation of prothrombin time by >3sec. 5.Hepatic decompensation due to HBV reactivation 6.Mortality 7.Mortality due to HBV reactivation	
			ALT (IU/L), mean (SD)	50.9(21)	51.8(22.9)				
			Total bilirubin (mg/dL), mean (SD)	0.92(0.39)	0.85(0.35)				
			AFP (ng/mL), median (range)	201.68(2-895.6)	110.3(2-1201.5)				
			Tumour size (cm), mean (SD)	6.4(3.7)	7.1(3.8)				
			Child pugh score (5/6)	29/7	28/9				
			Undetectable HBV DNA (<2x103 copies/mL) before treatment	9 (25)	10 (27)				
			No baseline differences between the two groups. All patients had genotype C.						
Median onset of hepatitis = 5.8 months during follow up HBV reactivation preceded the onset of hepatitis by a median of 3.3 weeks (0-60) weeks. Effect size									

	Preemptive lamivudine n=36	Control n=37
HBV reactivation, n (%)	1 (2.8)	15 (40.5)
Hepatitis, n (%)	6 (16.7)	16 (43.2)
Hepatitis due to HBV reactivation, n	1	11
Grade of hepatitis Moderate(ALT elevation 3-5xULN) Severe (ALT elevation >5xULN)	 3 3	 5 11
Hepatic decompensation, n (%) Hepatic decompensation due to HBV reactivation, n	1 (2.8) 0	5 (13.5) 3
Mortality, n Mortality due to HBV reactivation, n	4 0	3 1

All cases of clinical hepatitis (both treatment arms) were developed during a median follow up of 5.8 months.
For the preemptive group, 1 patient developed viral resistance 9 months after initiation of lamivudine therapy, but resumed TACL after switching to adefovir.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Huang 2009	Non-randomised controlled trial (with	32	Inclusion: patients with advanced or relapsed non-hodgkin's lymphoma undergoing high dose chemotherapy and autologous hematopoietic stem cell transplantation. HBsAg, HBcAb, HBeAg or HBeAb positivity, normal LFT before	Prophylactic lamivudine 100mg/day, 7 days	No prophylactic lamivudine (n=12)	At least 24 weeks after completion of	1.Hepatitis due to HBV reactivation -->10 fold	Not stated.

	the use of historical controls) China		transplantation, ALT and AST ≤2.5xULN, total bilirubin ≤1.25xULN, GGT ≤2.5xULN and albumin ≥30g/l, no evidence of HAV, HCV, HDV or HEV infection. Exclusion: decompensated liver disease at screening. Baseline characteristics	before and until at least 6 months (24 weeks) after transplantation (n=20)		HSCT	increase in HBV DNA when compared with baseline pre-chemotherapy value, or an absolute increase in HBV DNA of >105 copies/mL 2.All-cause mortality 3.Mortality due to hepatic failure 4.Resistance	

	Prophylactic lamivudine (n=20)	No prophylactic (n=12)
M/F	13/7	7/5
Mean age (SD)	37(12)	29(9)
Median ALT (range)	24.7(18-22)	25.5(10-100)
Median HBV DNA (copies/mL)	<103(<103-12.3x103)	<103(<103-5.12x103)
HBeAg positive*	17	4
Cycles of previous chemotherapy, median (range)	10.5 (5-20)	11 (6-16)
Underlying liver disease Asymptomatic Adiposis hepatica/ liver cirrhosis (compensation)	 18 2	 11 1

			*P=0.006					

Effect size

Median (range) duration of lamivudine: 6 (3-10) months.

Median time to onset of hepatitis
Prophylactic: 363 (360-366) days;
No treatment: 14.5 (3-114) days

	Prophylactic LAM n=20	No prophylactic n=12
Incidence of hepatitis due to HBV reactivation*, n (%)	2 (10)	6 (50)
Severity of hepatitis Mild (grade 1 +2) ≤5xULN Severe (grade 3 +4) >5xULN	 2 (10) 0 (0)	 3 (25) 3 (25)
Mortality* Mortality due to hepatic failure**	4 (20) 0(0)	7 (58.3) 3 (25)
Resistance	1	0

*P<0.05
**P=0.053

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Hui 2005A	Non-randomised trial (with historical controls) Sample size calculation given	33	Inclusion: HBsAg positive recipients (at recruitment) who underwent allogenic hematopoietic stem cell transplantation (bone marrow transplant) (HSCT) with HBsAg positive donors Exclusion: no coinfection with HCV Baseline characteristics No information given for the subgroup (HBsAg positive recipients	Prophylactic lamivudine (unclear dose), treated before marrow harvest and HSCT and continued for 52 weeks after HSCT (n=19)	No prophylactic lamivudine (n=14)	Median of 12 months in group 2 and 13 months in group 1	1.HBV related hepatitis -hepatitis (>3 fold elevation of ALT on two consecutive tests 5 days apart in the absence of systemic infections) that was preceded by HBV DNA elevation to >10 times compared to baseline, in patients who remained HBV DNA positive, if the serum HBV DNA turned from negative to positive	Cheng Si-yuan (China-International) Hepatitis Research Foundation

Effect size

	Prophylactic LAM n=19	No prophylactic lamivudine n=14
HBV related hepatitis, n	2	7
Cox proportional hazard regression model Reduction of HBV related hepatitis Hazard ratio	7.27 (1.62-32.58)*	1.00

*p=0.01

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Lau 2002	Non randomised trial	40	Inclusion: HBsAg positive patients who received allogeneic hematopoietic cell transplantation Exclusion: not stated Baseline characteristics	Prophylactic lamivudine (100mg/day), started 1 week before transplantati	Case matched (in terms of pretransplant ALT, HBV serology,	52 weeks after transplantation	1.Hepatitis >3 fold ALT elevation on 2 consecutive determinations, 5 days	Not stated

				Prophylactic LAM	No prophylactic LAM	on until 52 weeks after transplantation (n=20)	HBV genotype, HBV DNA) recipients who did not receive lamivudine (n=20)		apart, compared to baseline value, in the absence of systemic infections 2.Hepatitis due to HBV reactivation HBV DNA elevation to >10 times, compared to baseline value, plus the above. 3.All-cause mortality 4.Mortality related to hepatic failure	
			Median age (range)	38.5 (13-54)	32 (5-48)					
			M:F	10:10	16:4					
			Median ALT (range)	31.5 (1-102)	24 (10-86)					
			Recipient HBV serology HBeAg (+) Anti-HBe (+) HBV DNA positive	 4 16 9	 4 16 9					
			Mean HBV DNA (SD)	10 (8.7)	12.7 (4.6)					
			HBV genotype B C	 6 10	 6 10					
			Donor HBV serology HBsAg (+) Anti-HBs (+) Anti-HBc (+) HBV negative Mean HBV DNA (SD)	 9 4 3 7 58.9 (75.7)	 5 6 4 9 70.2 (104.7)					
Effect size										

	Prophylactic lamivudine n=20	No prophylactic lamivudine n=20
Hepatitis *	8	16
HBV related hepatitis*	1	9
Overall mortality	3	9
Mortality due to hepatic failure	0	2

*p=<0.05

Pre-emptive lamivudine therapy effectively reduces hepatitis due to HBV reactivation in HBsAg positive patients treated with allogeneic hematopoietic cell transplantation (multivariate cox proportional hazards regression model)

	Univariate hazard ratio (HR)	P value	Multivariate HR	P value
Preemptive use of lamivudine Yes No	 0.08 (0.01-0.62) 1	 0.016	 0.09 (0.01-0.69) 1	 0.021

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Chan et al, 2002. Preemptive lamivudine therapy based	Cohort study with historical contros (patients	N=67	Inclusion: HbsAg positive patients who underwent renal allograft transplantation. Immunosuppressive treatment after kidney transplantation:	Preemptive lamivudine (100mg/day) was started if patients	No preemptive treatment (n=52)	82 +/-58 months after transplantation	1.All-cause mortality 2.Mortality	Not stated

on HBV DNA level in HbsAg-Positive kidney allograft recipients	who underwent transplanation before January 1996 when the lamivudine become available.		Methylprednisolone 0.5g intravenously followed by prednisolone 30mg/d Cyclosporine 0.8mg/kg/d (azathioprine was used before cyclosporine availability) Steroid resistant rejection was treated with anti-thymocyte globulin or anti-CD3 antibody. Exclusion: patients positive for antibody to hepatitis C virus or hepatitis C virus RNA, who had significant alcohol consumption, patients with cirrhosis on biopsy or decompensated liver disease were excluded. Baseline characteristics 29 (43.3%) were HbeAg positive at the time of kidney transplantation 49 (73.1%) had at least one episode of elevated ALT after kidney transplantation Among the 15 patients who received lamivudine, 3 were late referrals who received lamivudine as salvage therapy after the development of liver decompensation-these 3 patients were excluded from between group comparisons.	satisfied either criteria:1) HBV DNA>2.83x108 copies/ml in patients with normal ALT or 2) HBV DNA>2.83x107 copies/ml in patients with increased ALT and/or a liver biopsy showing significant hepatitis (n=15)		(range 13-212 months)	due to liver complications	

The median duration of lamivudine treatment was 190 days (range 85-385) for the prophylactic group and 139 days (range 17-276) for the therapeutic group.

Effect size

	Preemptive lamivudine (N=12)	No preemptive lamivudine (N=57)
Overall mortality	0/12	14/52
Mortality due to liver complications	0	8/52

E.6.7 Pregnant women

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Xu WM, Cui YT, Wang L et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled	Double blinded multicenter RCT in China and Philippines	N=155 (randomised) N=155 (ITT) N=150 (as treated)	Mothers aged 16 and over with an estimated gestational age of 26-30 wks at screening who had detectable serum HBsAg and serum HBV DNA > 1000 MEq/mL [branched-DNA (bDNA) Quantiplex Assay, Chiron Diagnostic, Emeryville, CA, USA, lower limit of detection (LLOD) of 0.7 MEq/mL or ~ 105 copies/mL; 1 MEq/mL ≡ 106 copies/mL]. Subjects were excluded if they were co-infected with hepatitis C virus, hepatitis delta virus, or were known to be infected with HIV. Subjects were also excluded if they had serum alanine aminotransferase (ALT) levels > 10 times the upper limit of normal for the reference range (ULN) at screening or had a history of acute hepatitis exacerbations resulting in transient decompensation; or had decompensated liver	1st group: lamivudine (100mg/day) from week 32 of gestation to week 4 postpartum + infants vaccine + HBIG (N=63) Drop-outs for mothers	Placebo + Vaccine + HBIG (N=62) Drop-outs for mothers prior to delivery: 2/62 -59 infants at birth - N infants at 52	12 weeks post delivery for mothers and 52 weeks post birth for infants	Critical outcomes: Newborns and infants (12, 28 and 52 weeks) HBsAg positivity Newborns and infants (12, 28 and 52 weeks) HBV DNA positivity Secondary outcomes: Maternal HBV	GlaxoSmithKline Research and Development

study. J Viral Hepat. 2009; 16(2):94-103.
XU2009

disease defined as serum bilirubin level > 2.5 x ULN (except for Gilbert's syndrome), prothrombin time > 3 s prolonger, serum albumin below the lower limit of normal for the reference range, or history of ascites, variceal haemorrhage or hepatic encephalopathy. Finally subjects were excluded if they had anaemia, leucopenia and granulocytopenia, thrombocytopenia, a serum creatinine > 1.5 mg/dL, or evidence of pancreatitis

	Lamivudine (N=89)*	Placebo (N=61)**
Age (yrs) median (range)	26 (19-32)	25 (20-36)
Ethnic origin, Asian – n (%)	89 (100)	61 (100)
Positive for HBeAg – n (%)	88 (99)	61 (100)
Abnormal ALT – n (%)	14 (16)	8 (13)
Serum HBV DNA – Meq/mL*** Median Range Mean (SD)	 1936.0 0.4-10030.0 2220.0 (1610.9)	 2390.0 629.6-7577.0 2692.7 (1627

As treated population

* Lamivudine = lamivudine + vaccine + HBIG group and Lamivudine + Vaccine group

** Placebo = Placebo + Vaccine + HBIg group

*** Nineteen mothers (12 lamivudine and seven placebo) were enrolled with HBV DNA results at

prior to delivery: 5/63

-56 infants at birth

- N infants at 52 weeks=49

2nd group: lamivudine (100mg/day) from week 32 of gestation to week 4 postpartum + infants vaccine + (N=30)

Drop-outs for mothers prior to delivery: 2/30

-26 infants at birth

- N infants at 52 weeks=21

This arm was

weeks=41

DNA reduction

Adverse events (mothers, infants)

Congenital abnormalities

			screening either missing or < 1000 MEq/mL. At baseline, only nine of these mothers (five lamivudine and four placebo) had HBV DNA levels that were < 1000 MEq/mL. Of these, one lamivudine mother (baseline HBV DNA value of 724.8 Meg/mL) and four placebo mothers (Baseline HBV DNA values of 873.0, 855.7, 899.7 and 629.6 MEq/mL) had an infant included in the primary analysis Demographic and baseline characteristics of infant	discontinued . Results are not presented for this arm				

	Lam + Vacc + HBIg (N=56)	Placebo + Va + HBIg (N=59
Gestational age, wks, median (range)	39 (27-41)	39 (33-41)
Gender, male n (%)	35 (63)	34 (58)
Weight, kg, median (range)	3.2 (2-5)	3.3 (2-5)
Vaginal delivery n (%)	24 (43%)	24 (41%)
Caesarean section n (%)	32 (57%)	35 (59%)

Efficacy newborns/infants

	Lamivudine + Vaccine + HBIg	Placebo + Vaccine + HBIg	P value

HBsAg seropositivity at birth	17/56 (30)	14/59 (24)	0.480
HBsAg seropositivity at week 12**	4/56	6/59	0.466
HbsAg seropositivity at week 28**	3/56	6/59	0.250
HbsAg seropositivity at week 52***	10/49	23/41	-
HBV DNA seropositivity at birth	7/56 (13)	24/59 (41)	0.001
HBV DNA seropositivity at week 12**	11/56	14/59	0.547
HBV DNA seropositivity at week 28**	6/56	9/59	0.249
HBV DNA seropositivity at week 52***	4/49	9/41	-
Adverse events	10/56 (1 drug related-jaundice)	12/59 (1 drug related-hyperbilirubinaemia)	-
Serious adverse events (none thought to be drug related)	5/56	3/59	

** ITT analysis as no information on drop outs for this follow up
*** ACA

Efficacy for mothers

	Lamivudine + Vaccine + HBIg (N=89)*	Placebo + Vaccine + HBIg (N=61)
HBV DNA maternal mean reduction (baseline- during delivery)^	2168 Meq/mL	529.9 Meq/mL

Adverse events	7/89 (1 adverse event was considered to be drug related)	6/61
Serious adverse events (none thought to be drug related)	1/89	1/61

*Included the 2nd group of lamivudine + only vaccine that is not reported for the infants outcomes.

^ the results derived by substracting the measurements during labour and delivery from the baseline figures- therefore SD couldn't be calculated.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Li XM, Yang YB, Hou HY et al. Interruption of HBV intrauterine transmission: a clinical study. World Journal of Gastroenterology. 2003; 9(7):1501-1503.LI2003	RCT (no other information related to study desing) in China	N=151 (patients were randomised to 3 groups: HBIG group, lamivudine group and no treatment group).	Pregnant women who were HBsAg positive with normal liver and kidney function. Serial tests were negative for HAV, HCV, HDV and HEV and no other severe complications were found and no other drugs, including the ones studied, anti-virus, cytotoxic, steroid hormones, or immune regulating drugs were administered. No significant differences were found in age, race, time of gestation and parturition, gestational age, way of delivery, and incidence of threatened abortion, threatened labour or pregnancy-induced hypertension syndrome. The 151 women delivered 151 newborns.	Lamivudine 100mg daily from 28 week of gestation till the 30th day after labour (N=43)	HBIG 200 IU intramuscularly was administered from 28 weeks of gestation once every 4 weeks until labour (N=56). No therapy (N=52)	Until labour.	Critical outcomes: Newborns HBsAg positivity Newborns HBeAg positivity Newborns HBV DNA positivity Secondary outcomes: Maternal HBV DNA reduction (after administration of agents) Adverse events	None reported

							(mothers, infants)	

Efficacy for newborns

	Lamivudine (n=43)	HBIG (n=56)	No therapy (n=52)
HbsAg seropositivity at birth	1/43	3/56	8/52
HbeAg seropositivity at birth	7/43	7/56	11/52
HBV DNA seropositivity at birth	7/43	9/56	17/52

Efficacy for mothers

	Lamivudine (mean, SD)	HBIG (mean, SD)	No therapy (mean, SD)
Maternal HBV DNA reduction (after administration of agents) log 10 copies/ml	2.16 (1.27)	2.09 (2.28)	0.82 (2.73)

Adverse events

No incidences were detected throughout administration or follow-up. No significant differences in gestational age, severity of pospartum hemorrhage, rate of cesarean section, neonatal weight, neonatal height,circumference of neonatal heald and Apgar score (P>0.05).

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Yu M. The efficacy	Prospective cohort	185	Inclusion: Pregnant women who visited and delivered in the hospital between June 2006 and	Lamivudine 100mg (N=100)	Controls or no	12 mont	At birth, 1 month and	Not stated

and safety of antiviral therapy with lamivudine to stop the vertical transmission of hepatitis B virus. Eur J Clin Microbiol Infect Dis. 2012		All infants were given 200 IU of HBIG injection immediately after birth and at day 15, as well as 20µg of genetically engineered hep B vaccine immediately after birth and at month 1 and 6. Blood samples were taken from the femoral vein of the infants after birth before prophylactic immunisation, and at months 1,7, and 12	March 2009. Age between 20 and 40 years, gestation period between 24 and 32 weeks, HBsAg/HBeAg positivity, HBV DNA ≥1.0 x 107 copies/ml, normal or abnormal serum ALT at baseline, and husbands negative for HBsAg/HBeAg/HBVDNA. Exclusion: Ultrasonography showing fetal abnormality; ever threatened abortion, threatened premature labor, defective immunological function, having co-infection with hepatitis A, C,D, E or HIV virus; severe malnutrition, diabetes or kidney disease, using drugs which can affect immune function or antiviral drugs within 6 months. Baseline characteristics <table><tr><td></td><td>Lamivudine (n=94)</td><td>Controls (n=91)</td></tr><tr><td>Age, mean (SD)</td><td>26.64 (4.17)</td><td>25.78 (3.89)</td></tr><tr><td>Weight (kg), mean (SD)</td><td>71.43 (13.98)</td><td>70.75 (11.53)</td></tr><tr><td>Abnormal ALT, n (%)</td><td>48 (51.06)</td><td>45 (49.45)</td></tr><tr><td>HBV DNA (copies/ml)</td><td>7.63 (0.54)</td><td>7.71 (0.71)</td></tr><tr><td>E antigen titers, mean (SD)</td><td>1376.23 (428.85)</td><td>1421.57 (466.63</td></tr></table>There were no significant differences in the above parameters between the two groups at baseline.	From the 24th to 32nd week of gestation (2nd and last trimester), which was continued after childbirth till satisfactory efficacy or drug resistance mutation appeared if serum ALT was abnormal (≥40U/L) at baseline or stopped treatment after one month of post-natal if serum ALT was normal at baseline N=94 completers 6 patients did not complete follow up.	lamivudine (was only treated with glycyrrhizin, reduced glutathione, and polyunsaturated lecithin choline as well as the intervention group if ALT was abnormal) N=91 completers. 9 patients did not complete follow up.	hs	12 months follow up after birth. Critical outcomes: 1) newborns and infants HBV DNA positivity 2) newborns and infants HBsAg positivity 3) Maternal undetectable HBV DNA (<5x102 copies/ml to 1x 109 copies/ml) prior to delivery 4) childrens adverse 5) Congenital abnormalities	

		to detect levels of HBVM and HBV DNA.						

Effect size

	Lamivudine (n=94)	Controls (n=91)	P value
Maternal undetectable HBV DNA (negativity), n (%)			
Before delivery	29 (30.85)	0(0)	0.000
Maternal log HBV DNA, mean (SD)			
4 weeks	4.56 (1.52)	7.74 (0.71)	0.000
8 weeks	3.74 (1.43)	7.83 (0.52)	0.000
Before delivery	3.18 (1.52)	7.81 (0.76)	0.000
Newborns			
Serum HBV DNA positivity	0/94	-	
HBsAg positivity	9/94	29/91	
At 1 month after birth			
HBsAg positivity	0/94	10/91	
HBV DNA positivity	0/94	10/91	
Infants (at 12 months follow up)			
HBsAg positivity	0/94	7/91	
HBV DNA positivity	0/94	7/91	
HBeAg positivity	-	7/91	
Adverse event			
Elevated creatine kinase, n	1	0	-
Postpartum hemorrhage n (%)	33 (35.11)	36 (39.56)	0.53

Cesarean section n (%)	48 (51.06)	45 (49.45)	0.83
Preterm birth n (%)	7 (7.45)	8 (8.79)	0.74
Neonatal asphyxia n (%)	4 (4.26)	6 (6.59)	0.48
Malformation n (%)	0 (0)	1 (1.1)	0.31

Authors' conclusion: Lamivudine treatment can effectively and safely stop vertical transmission of HBV and normalise the ALT levels of pregnant women.

Notes: study limitation, double blind randomisation was not adopted due to the requirement of informed consent from both the investigators and subjects.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Han 2011. A prospective and open-lable study for the efficacy of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus	Open label prospective case control study from a single tertiary hospital in China between December 2007 and August 2009	N=229	Inclusion: HbeAg positive pregnant aged 20-40 years, gestational age between 20-32 weeks, women with CHB, levels of HBV DNA>107 copies/mL. Eligible patients were enrolled to the treatment or observation group based on patient's informed decision about the risks and benefits of telbivudine therapy vs clinical observation. Exclusion: coinfection with hepatitis A, C,D, E or HIV; evidence of hepatocellular carcinoma, decompensated liver disease, or significant renal, cardiovascular, respiratory or neurological comorbidity; concurrent treatment with immune modulators, clinical signs of threatened miscarriage in early pregnancy, use of previous antiviral therapy, evidenceof fetal deformity or if the biological father had CHB. Baseline characteristics | | Telbivudine | No therapy | P val	Telbivudine (600 mg) starting in the 2nd or 3rd trimester (n=135) (136 infants were born) All mother were reported to Antiviral Pregnancy Registry. Mother were instructed not to breast-feed	No treatment (n=94) 88 mother-infant pairs completed all follow up visits	Every 6- 8 weeks prior to delivery and then at postpartum week 28.	1) newborn and infant (28 weeks) HBV DNA positivity 2) newborn and infant (28 weeks) HbsAg seropositivity 3) maternal undetectable HBV DNA (<500 copies/ml)	Department of Health, Jiangsu Province, People's Republic of China

infection. Journal of Hepatology 2011:55; 1215-1221.								4) congenital anomalies 5) serious adverse events	

	(600 mg/day) (n=135)	(n=94)	
Median age (range)	27 (20-38)	26 (20-33)	0.62
Previous pregnancy, n (%)	2 (1-5)	2 (1-5)	0.93
Median serum HBV DNA (range), log10 copies/ml	8.16 (7.04-9.45)	8.00 (7.08-9.53)	0.12
Median serum ALT (range), U/L	22.35 (8.20-334.90)	27.6 (8.10-262.5)	0.22
Infants: -Gestational age (weeks), median (range) -Sex, male, n (%) - Brith weight, kg, median (range) - Birth length, cm, median (range) - Apgar score of 5 min, median (range)	 -39 (34-41) -74 (54%) -3.3 (1.81-4.55) -50 (44-57) -10 (9-10)	 -39 (33-41) -44 (47%) -3.35 (1.75-4.15) -50 (43-53) -10 (9-10)	 0.74 0.28 0.25 0.96

All infants were vaccinated with genetically enginneered HBV vaccine 20µg according to a standrd vaccination regimen (within 12 hours of birth and weeks 4 and 24) and hepatitis B immune globulin 200 IU within 2 hours after

infants when they received telbivudine therapy.

132 mother-infant pairs completed all follow up visits

Effect: two years of specified study intervention

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			birth and on day 15.					

Effect size

Critical outcomes for newborn/infants	Telbivudine (600mg/d) (n= 136)	No therapy (n=94)	p value
At birth			
HbsAg positive	13 (10%)	28 (30%)	-
HBV DNA positive	123 (90%)	75 (80%)	-
At 28 weeks			
HbsAg positive	0/132	7/88 (8%)	-
HBV DNA detectable	0/132	7/88 (8%)	-
Low birth weight	1/136	1/94	
Congenital anomalies	0	0	
Serious adverse events	0	0	
Pneumonia, n (%)	6/136	5/94	

Critical outcomes for mothers	Telbivudine (600mg/d) (n=135)	No therapy (n=94)	p value
Prior to delivery: HBV DNA<500 copies/ml	44 (33%)	0 (0%)	<0.001
Adverse events, n (%)	12/135 (8.9%)	5/94 (5.3%)	0.311
Cesarean section, n (%)	75 (56%)	44 (47%)	0.192

Authors' conclusion: Telbivudine used during pregnancy in CHB HbeAg+ highly viremic mothers can safely reduce perinatal HBV transmission. Telbivudine was well tolerated with no safety concerns in the telbivudine-treated mothers or their infants on short term follow up. These data support the use of telbivudine in this special

population.

Notes:

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Pan 2012. Telbivudine prevents vertical transmission from HbeAg positive woment with chronic hepatitis B. Clinical Gastroenterology and Hepatology 2012:10; 520-526.	Open label prospective case control study from a single tertiary hospital in China from August 2008-December 2009.	N=88	Inclusion: HbeAg positive pregnant aged 20-40 years, gestational age between 12-30 weeks, women with CHB, levels of HBV DNA>6 log10 copies/mL and increased levels of ALT (>1x times the upper limit of normal (ULN=40 IU/mL) and <10 times ULN). Eligible patients were enrolled to the treatment or observation group based on patient's informed decision about the risks and benefits of telbivudine therapy vs clinical observation. Exclusion: coinfection with hepatitis A, C,D, E or HIV; evidence of hepatocellular carcinoma, decompensated liver disease, or significant renal, cardiovascular, respiratory or neurological comorbidity; concurrent treatment with immune modulators, cytotoxic drugs, or steroids, clinical signs of threatened miscarriage in early pregnancy, use of antiviral therapy within 6 months prior to the pregnancy; evidence of of fetal deformity or if the biological father had CHB. Baseline characteristics Telbivudine (600 mg/day) (n=53) | No therapy (n=35) | P val Median age (range) | 27 (21-34) | 27 (21-33) | 0.81	Telbivudine (600 mg) starting in the 2nd or 3rd trimester (n=53) (54 infants were born) All mother were reported to Antiviral Pregnancy Registry. Mother were instructed not to breast-feed infants when they received telbivudine therapy. 52 mother-	No treatment (n=35) 32 mother-infant pairs completed all follow up visits	Every 6- 8 weeks prior to delivery and then at postpartum week 4, 8, 16 and 28.	1) newborn and infant (28 weeks) HBV DNA positivity 2) newborn and infant (28 weeks) HbeAg seropositivity 3) newborn and infant (28 weeks) HbsAg seropositivity 4) maternal undetectable HBV DNA (<500 copies/ml) 5) congenital anomalies	Department of Health, Jiangsu Province, People's Republic of China

			Previous use of antiviral, n (%)	10 (19%)	0	0.00	infant pairs completed all follow up visits (13 stopped therapy after delivery)			6) serious adverse events	
			Median serum HBV DNA (range), log10 copies/ml	8.08 (6.62-9.45)	8.08 (6.76-9.08)	0.99					
			Median serum ALT (range), U/L	60.4 (41.4-422.0)	63.2 (42.4-262.5)	0.07					
				130 (35-400)	122 (62-309)						
			Infants: -Gestational age (weeks), median (range) -Sex, male, n (%) - Brith weight, kg, median (range) - Birth length, cm, median (range) - Head circumference (cm) - Vaginal delivery, n (%) - Ceserean section, n (%)	 -39 (34-41) -26 (48%) -3.2 (2.4-4.4) -50 (47.5-53) -33 (29-35) -20 (38%) -33 (62%)	 -39 (36-42) -16 (46%) -3.4 (2.8-4.2) -50 (48--53) -33 (31.5-35.5) -16 (46%) -19 (54%)						
			All infants were vaccinated with genetically enginneered HBV vaccine 20µg according to a standrd vaccination regimen (within 12 hours of birth and weeks 4 and 24) and								

			hepatitis B immune globulin 200 IU within 2 hours after birth and on day 15.					

Effect size

Critical outcomes for newborn/infants	Telbivudine (600mg/d) (n= 54)	No therapy (n=35)	p value
At birth			
HbeAg positive	54 (100%)	35 (100%)	
HbsAg positive	2 (4%)	8 (23%)	0.012
HBV DNA detectable	0	3 (9%)	0.029
At 28 weeks			
HbeAg positive	0	3 (9.7%)	0.029
HbsAg positive	0	3 (9.7%)	0.029
HBV DNA detectable	0	3 (9.7%)	0.029
Congenital anomalies	0	0	
Serious adverse events	0	0	
Pneumonia	3/52	1/32	

Critical outcomes for mothers	Telbivudine (600mg/d) (n= 53)	No therapy (n=35)	p value
Prior to delivery			
HBV DNA<500 copies/ml	28 (53%)	0 (0%)	<0.001
At week 4 postpartum			
HBV DNA<500 copies/ml	31 (58%)	0	<0.001
At 28 weeks			
HBV DNA<500 copies/ml	31 (58%)	0	<0.001

Authors' conclusion: women with CHB given telbivudine during the second or third trimester of pregnancy have reduced rates of perinatal tranmission. Telbivudine produced no adverese events in mothers or infants by 28 weeks.

Notes:

E.7 Monitoring

E.7.1 HBeAg positive patients with detectable HBV DNA and normal ALT levels

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Chu 2007	Prospective follow up study	N=133	HbeAg positive patients with normal ALT level (0-36 U/L), no evidence of cirrhosis based on clinical grounds and liver ultrasonnography and no concomitant infection with hepatitis C or delta at the baseline and no antiviral therapy before entry or during follow up who had documented seroconversion from HbeAg to anti-Hbe. Baseline characteristics Total (n=133) / Men (n=75) / Women (n=58) Mean age: 28.2 (6.9) / 28.3 (6.4) / 28.2 (7.5)	Maximal ALT during HbeAg positive phase (immune clearance phase)	For a minimum of 1 year following HbeAg seroconversion	Reactivation of hepatitis B defined as raise to more than twice the ULN of ALT levels, accompanied by positive serum HBV DNA (>1.4 X 105 copies/ml) by hybridization assays.	By a grant fron National Science of Council of Taiwan.

			on entry in years (SD)					
			Genotype -B -C	 108 (81%) 25 (19%)	 64(85%) 11(15%)	 44(76%) 14(24%)		
			Interval from entry to HbeAg seroconversion (years)	4.6 (3.7)	4.6 (4.0)	4.5 (3.3)		
			Follow up duration following HbeAg seroconversion (years)	5.8 (4.2)	5.9 (4.3)	5.7 (4.1)		

Results:

The annual rate of reactivation of hepatitis B was 3.3%.

The cumulative probabilities orf reactivation of hepatitis B were 15.1%, 29.8% and 32.8% respectively after 5, 10 and 15 years of follow up.

Predictive models for reactivation of hepatitis B following HbeAg seroconversion

	Univariate analysis*		Multivariate analysis*▪	
Prognostic factors	Hazard ratio (95% C.I)	P value	Hazard ratio (95% C.I)	P value
Maximal ALT during HbeAg positive (immuno clearance) phase <2 x ULN 2-5 x ULN >5 x ULN	 1 (0.72-6.16) 3.01 (1.12-8.08)	 0.17 0.029	 1 (0.89-8.47) 3.57 (1.22-10.46)	 0.08 0.02

* Cox proportional hazards regression models.

▪ Multivariate analysis included the following predictive factors: age on entry, gender, genotype, interval from entry to HbeAg seroconverion (in years) and age at HbeAg seroconversion.

The authors concluded that ALT levels>5 x ULN during the HbeAg positive phase was correlated significantly with reactivation of hepatitis B after HbeAg seroconversion.

E.7.2 Inactive carriers with CHB (defined as HBeAg negative patients and normal ALT levels)

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Kumar 2009	Prospective cohort Monitoring factors measurement : adequate	N= 217	Recruitment/setting: Liver Diseases Follow up clinic, India between Jan 1996 and Jan 2007. Inclusion: HBsAg positive for at least the previous 6 months; no present or past evidence of any symptoms related to liver disease; follow up of ≥12 months and HBeAg negative, anti-HBe positive, and normal ALT (<40IU/L) at presentation. Exclusion: Hep C, D, A, E or HIV coinfection; decompensated liver disease (defined by serum bilirubin >2.5 times the ULN, prothrombin time >3seconds compared with control; serum albumin <2.5 g/dL; or a history of ascites, variceal hemorrhage, or hepatic encephalopathy; evidence of liver disease because of other etiology and patients who had alcohol, drug usage, or superinfection with hep C, D, A, or E	Biochemical tests were performed using routine automated techniques. The ULN for serum ALT was 40 IU/L. Serum HBV DNA were quantified using ultrasensitive hybrid capture assay by Digene co (lower limit of detection =	Median 69 months	Spontaneous ALT flare (ALT rose to > ULN x2 , accompanied by HBV DNA levels of ≥105 copies/mL or 100-fold rise in HBV DNA from the previous levels) Patients were stratified according to baseline ALT levels as low-normal ALT (<0.5 x ULN) and high-normal ALT (0.5-1 x ULN) Assessed every 3-6 months	Not stated

			that might be possible etiologic agents of ALT flare. Baseline characteristics N (%) Age, years (mean±SD): 35.3 ±13.4 Male, n (%): 161 (74.2) ALT (IU/L), median (range): 27 (11-40) Baseline HBV DNA (log 10 copies/ml), median (range): 4.75 (2.78-9.2) HAI, median (range)*: 4 (1-10) Fibrosis stage, median (range)*: 1 (0-4) Distribution of fibrosis stages, n (%): 0: 29 (25.7) 1: 41 (36.3) 2: 32 (28.3) 3: 10 (8.8) 4: 1 (0.9) Genotype, n (%) A: 49 (22.6) C: 3 (1.4) D: 149 (68.7) A+D: 16 (7.4) Precore mutant, n (%): 87 (40.1) BCP mutant, n (%): 51 (23.5)	4700 copies/mL). In patients with undetectable HBV DNA by quantitative PCR was used (lower limit of detection = 600 copies/mL).			
Results:							

During a median of 69 months follow up, 43 developed spontaneous ALT flares and 173 had no flare.

Annual rate of ALT flares was 4.3%.

The cumulative probabilities of ALT flare were 10.8% and 47.3%, respectively, after 5 and 10 years of follow up.

Median time to spontaneous ALT flare after enrolment into the study was 25 months (range, 1-128 months). The 10th percentile was 3.4 months. If the frequency of follow up is kept at 3 months, approximately 90% of ALT flares can be detected (table 1)

Table 1. Time to spontaneous ALT flare after enrolment (Median: 25 months (range1-128months)

Percentiles	Time (months)
5	2.2
10	3.4
15	5.0
20	5.0
25	6.0
30	9.6
35	14.0
40	19.0
45	23.2
50	25.0
55	34.4
60	39.2
65	54.0
70	62.0
75	67.0
80	70.0
85	77.0
90	97.2
95	116.4

100	128.0

Author's conclusion: A follow up every 3 months can capture up to 90% of flares and would help identify patients who require antiviral therapy.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Feld 2007	Prospective cohort Monitoring factors measurement : adequate Small sample size	N= 37	HBeAg negative with normal ALT (≤40IU/mL) at entry Recruitment/setting: Toronto Western Hospital Liver Clinic between Jan 2001 and Aug 2003. Inclusion: serum HBsAg positive for at least 6 months. Asymptomatic CHB patients who were HBeAg negative, anti-HBe positive, had normal ALT levels Also reported on other subgroups: HBeAg negative patients with abnormal ALT, HBeAg positive patients Exclusion: patients coinfected with Hep C, D, HIV and other known causes of liver disease, patients receiving HBV treatment. Baseline characteristics N (%) Median age, years (range): 48.9 (23-67)	ALT levels HBV DNA levels Measured by the Roche PCR assay (detectable range: 500- 200,000 copies/mL) Assessed every 3 months	Median 3 years, range: 0.67-4.0	ALT elevation (a change from normal ALT to elevated ALT) (40IU/mL) from one visit to the next ALT normalisation (a change from elevated ALT to normal ALT) (≤40IU/mL) from one visit to the next Statistical method: Time to event for both Kaplan meier	Not stated

			Male, n (%)	26 (70.3)				and Cox regression analyses were counted o the basis of the time at which the patient became at risk (ALT normalisation) and the time of the event (ALT elevation).	
			Ethnicity Asian African Caucasian Other	 27 (73.4) 1 (2.7) 12 (32.4) 2 (5.4)					
			Histology F0 F1 F2 F3 F4	 3 (8.1) 4 (10.8) 7 (18.9) 2 (5.4) 11 (29.7)					
			Genotype A B C D E F Undetermined*	 6 (16.2) 11 (29.7) 9 (24.3) 6 (16.2) 1 (2.7) 0 4 (10.8)					
			Baseline ALT (IU/L)	24.9 ± 6.5					
			Baseline HBV DNA (log copies/mL)	4.91 ± 1.9					
			Baseline HBV DNA <10,000 10,000-30,000 30,001-50,000 50,001-100,000 100,001-200,000 >200,000	 18 (48.6) 4 (10.8) 2 (5.4) 8 (21.6) 2 (5.4) 3 (8.1)					

			*not genotyped because of consistently undetectable HBV DNA				

Results:

The corresponding HBV DNA level was helpful in predicting the likelihood of future ALT elevation, particularly in the first year of follow up (N=37).

Within one year of follow up	ALT elevation (40IU/mL)
At baseline	
HBV DNA >10,000 copies/mL and normal ALT	43%
HBV DNA <10,000 copies/mL	2.9%

With longer follow up, although patients with HBV DNA >10,000 copies/mL and normal ALT were still more likely to develop an increased ALT, an increasing proportion of those with low HBV DNA also had ALT elevation.

By the end of follow up (median 3 years):

At end of follow up (median 3y)	ALT elevation
At baseline	
HBV DNA >10,000 copies/mL and normal ALT	77.6%
HBV DNA <10,000 copies/mL	37.6%

Different HBV DNA thresholds used (% taken from graph):

	ALT elevation over time (>40IU/mL)
At 6 months	
HBV DNA >30,000 copies/mL + normal ALT	23%
HBV DNA <30,000 copies/mL + normal ALT	8%
At 12 months	
HBV DNA >30,000 copies/mL + normal ALT (n=14)	40%

HBV DNA <30,000 copies/mL + normal ALT (n=27)	19%
At 36 months	
HBV DNA >30,000 copies/mL + normal ALT (n=3)	70%
HBV DNA <30,000 copies/mL + normal ALT (n=5)	60%

	ALT elevation over time (>40IU/mL)
At 6 months	
HBV DNA >50,000 copies/mL + normal ALT	26%
HBV DNA <50,000 copies/mL + normal ALT	9%
At 12 months	
HBV DNA >50,000 copies/mL + normal ALT (n=12)	44%
HBV DNA <50,000 copies/mL + normal ALT (n=29)	18%
At 36 months	
HBV DNA >50,000 copies/mL + normal ALT (n=3)	68%
HBV DNA <50,000 copies/mL + normal ALT (n=5)	61%

	ALT elevation over time (>40IU/mL)
At 6 months	
HBV DNA >100,000 copies/mL + normal ALT	41%
HBV DNA <100,000 copies/mL + normal ALT	6%
At 12 months	
HBV DNA >100,000 copies/mL + normal ALT (n=4)	68%
HBV DNA <100,000 copies/mL + normal ALT (n=37)	17%
At 36 months	
HBV DNA >100,000 copies/mL + normal ALT (n=2)	68%
HBV DNA <100,000 copies/mL + normal ALT (n=6)	62%

	ALT elevation over time (>40IU/mL)

At 6 months	
HBV DNA >200,000 copies/mL + normal ALT	42%
HBV DNA <200,000 copies/mL + normal ALT	10%
At 12 months	
HBV DNA >200,000 copies/mL + normal ALT (n=3)	58%
HBV DNA <200,000 copies/mL + normal ALT (n=38)	21%
At 36 months	
HBV DNA >200,000 copies/mL + normal ALT (n=2)	66%
HBV DNA <200,000 copies/mL + normal ALT (n=6)	58%

At 1 year of follow up, more patients with normal ALT and HBV DNA above either 30,000 or 50,000 copies/mL thresholds developed an ALT elevation, than those with HBV DNA below those thresholds (p=0.039). The discriminating value disappeared with longer follow up (p=0.093).

Thresholds of 30,000 or 50,000 copies/mL were less discriminating than10,000 copies/mL.

A threshold of 100,000copies/mL was able to discriminate between those who would experience an ALT elevation and those who would not during the first year of follow up. Data were limited because a small number of patients had HBV DNA above this level with normal ALT.

Factors predicting future ALT elevation or in HBeAg negative patients (cox proportional hazards regression):

Factors	Adjusted HR
Number of previous ALT elevations	1.77 (1.03-3.03)*

*adjusted for HBV DNA threshold of 10,000 copies/mL.

**adjusted for baseline ALT and previous ALT elevations.

Factors predicting future ALT normalisation in HBeAg negative patients (cox proportional hazards regression):

Factors	Adjusted HR*
Number of previous ALT normalisation	2.44 (1.07-5.57)

*adjusted for other covariates significant according to univariate analysis.

Potential study limitations:

ALT, used as a marker for liver disease activity. Repeated liver biopsies (to truly identify active liver disease) in such a short time would be unacceptable.

Only patients with high ALT and low HBV DNA underwent a liver biopsy.

Author's conclusion: HBeAg negative patients have a fluctuating course. HBV DNA values <10,000 copies/mL predict persistently normal ALT for at least 1 year. Patients with HBV DNA values 10,000-100,000 copies/mL can safely be followed at 6 monthly intervals, whereas HBV DNA >100,000 copies/mL are highly predictive of future ALT elevation and should prompt regular follow-up. This data suggest that decisions should not be made on the basis of one single measurement. If patients were presumed to be inactive and are only followed only intermittently, asymptomatic flares might be missed and this leads to the silent progression of liver disease. .

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Arai 2012	Retrospective	423	All patients visiting the Chiba University Hospital and who were HBsAg positive carriers (persistent HBV infection). Patients who were positive for the HCV antibody and those who had another potential cause for chronic liver disease were excluded. Patients who were monitored for <1year or who had been given antiviral drugs before entry were also excluded. Baseline characteristics Total (n=423) / HBsAg seroclearance (n=25) / No HBsAg seroclearance / P value Sex (male/ female): 239/184 / 18/7 / 221/177 / NS Age years, mean (SD): 40.5 (13.8) / 44.6 (9.4) / 40.2 (14) / NS HBeAg status (+/-): 183/240 / 3/22 / 180/218 / 0.003 HBV DNA (log copies/ml): 5.6 (1.9) / 4.6 (1.8) / 5.6 (1.9) / 0.007	Quantitative HBsAg , every 6-12 months	Average 6.5±5.7 years	Cut off <0.03IU/mL indicates HBsAg seroclearance	Not stated

			ALT (IU/L)	72.7 (90.4)	116.3 (206.1)	69.9 (76.8)	NS				
			Genotype A/B/C/D/ undetermined	5/31/261/1/ 125	1/2/18/0 /4	4/29/243 /1/121	NS				
			Past use of interferon	16/407	2/23	14/384	NS				
			HBsAg (log10 IU/mL)	3.37 (1.21)	2.47 (1.28)	3.44 (1.13)	0.001				

Results:

Cox regression analysis - predictive models for reactivation of hepatitis B surface antigen seroclearance (mean follow up of 6.5 years)

	Univariate analysis*		Multivariate analysis*▪	
Prognostic factors (at baseline	Hazard ratio (95% C.I)	value	Hazard ratio (95% C.I)	P value
HBV DNA				
High HBV DNA	1.0		1.0	
Low HBV DNA	0.58 (0.46-0.75)	<0.001	0.94 (0.66-1.35)	NS
HBsAg (log)				
High HBsAg	1.0		1.0	
Low HBsAg	0.39 (0.29-0.53)	<0.001	0.45 (0.29-0.70)	<0.001

*covariates in multivariate analysis were not reported.

Authors' conclusion: The predictive factor for the seroclearance of HBsAg was a lower level of HBsAg. Therefore, measurements of HBsAg levels are one of the most effective means to follow up HBV carriers accurately.

E.7.3 Patients with CHB on interferon or pegylated interferon treatment

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Heijink 2000	Prospective controlled multicenter trial (EUROHEP); 1st phase: eligible patients received 10MU of INF-a three times per week for 16 weeks ("standard therapy"). 2nd phase: non responding patients of the "standard 16 week therapy" entered in the second phase of the study and were randomized to receive no further	N=162 Response rate 139/162 Missing data from 1st phase: 16 patients discontinued therapy, 1 was retrospectively found that he has HBV DNA negative at start, 6 patients had insufficient serums. Missing data from 2nd phase: 1 patient in control group and three patients in	Patients (18-70 yrs old) with positivity in serum for at least 6 months, presence of HbeAg and HBV DNA in serum, as documented on 3 occasions in the 3 months before entry and histological evidence of chronic hepatitis on a liver biopsy taken in 6 months preceding enrollment. Exclusion criteria: hepatitis delta, C, or HIV, recent alchohol or drug addiction, previous IFN-A couse with a minimum duration of 12 weeks using at least 30MU per week, any antiviral or immune modulatory therapy in the last 6 weeks, immunocompromised patients, pregnancy, females of fertile age with inadequate contraception, significant medical illness	1)HbeAg levels indicated by AxSYM (<0.7PEI U ml-1) 2)HBV DNA measured by the Abbott HBV DNA assay (<=1.6 pg ml-1)	4, 8 and 16 weeks for the 1st phase/ 4, 8, 16 and 52 weeks for the 2nd phase	Response: simultaneous negative result for HbeAg and HBV DNA (<=1.6 pg ml-1)	None

	treatment ("controls", n=57), or a further 16 weeks of treatment ("prolonged theraphy", n=61).	the "prolonged therapy" group were unable to be evaluated due to insufficient serum.					

Results:

	"Standard therapy group"			
Prognostic factors	Responders at 16 weeks of INFa therapy (n=25)	Non responders at 16 weeks of INFa therapy (N=114)	P value (from univariate analysis)	P value (from multivariate analysis)
HbeAg (PEI Uml-1) geometric mean titres (GMT) 4th week after starting of INFa treatment 8th after starting of INFa treatment	 10* 6.5*	 700* 400*	 P=0.001 P=0.001	The authors mentioned that HbeAg decrease from the start of therapy to week 8 were the most important factors determining response with no mention on statistical significant.
HBV DNA (pg ml-1) geometric mean titres (GMT) 4th week after starting of INFa treatment 8th after starting of INFa treatment	 7.6* 5.0*	 40* 20*	 NS NS	The authors mentioned that this factor did not add any predictive value to response at week 16.

* Figures are taken from graphical presentation so maybe an approximation of the actual values.

The authors also gave results on the effect of HbeAg decrease during the first 8 weeks of therapy on the response rate at the end of "standard therapy" (end of 16 weeks) given for three abitarily chosen pretreatment HbeAg levels

Pretreatment HbeAg levels	Decrease by 50% in HbeAg levels during the first 8 weeks	Decrease by 90% in HbeAg levels during the first 8 weeks	Decrease by 99% in HbeAg levels during the first 8 weeks
	Response rate at the end of 16 weeks		
50 PEI U ml-1	26%	42%	78%

500 PEI U ml-1	8%	18%	44%
5000 PEI U ml-1	2%	6%	20%

	"Prolonged therapy group"		
Prognostic factors	Responders at 52 weeks of INFa therapy (previously non responders at 16-week of treatment) (n=16)	Non responders at 52 weeks of INFa therapy (previously non responders at 16-week of treatment) (n=42)	P value (from univariate analysis)
HbeAg (PEI Uml-1) geometric mean titres (GMT)			
4th week after starting of INFa treatment	100*	888*	P<0.01
8th week after starting of INFa treatment	61*	600*	P<0.01
16th week after starting of INFa treatment	9*	420*	NS

* Figures are taken from graphical presentation so maybe an approximation of the actual values.

	"Control group"		
Prognostic factors	Responders at 52 weeks (previously non responders at 16-week of treatment but received no further treatment) (n=6)	Non responders at 52 weeks (previously non responders at 16-week of treatment but received no further treatment) (N=50)	P value (from univariate analysis)
HbeAg (PEI Uml-1) geometric mean titres (GMT)			
4th week after starting of INFa treatment	642*	771*	NS
8th week after starting of INFa treatment	71*	578*	P<0.01
16th week follow up	39*	391*	NS

* Figures are taken from graphical presentation so maybe an approximation of the actual values.

Additional results:

The authors stated that changes in HBV DNA from the start of therapy to week 4 or 8 were not significantly related to response at week 52. No further data were given.

The authrs also reported that pretreatment HbeAg and HBV DNA levels were significantly related to response at 16 weeks but not related to response at 52 weeks.

Author's conclusions: As the pretreatment HbeAg level and the decrease of HbeAg in the first 8 weeks of INF therapy are clearly related to response, the study may have identified cessation criteria that allow to stop therapy in patients who have a high probability of non response.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Janssen 1994	Prospective follow up	N=12	Patients HbeAg and HBV DNA positive were followed longitudinally during interferon alpha therapy (5 MU daily, in courses of 1 and 4 monts duration, separated by 1 mount of rest).	1) HbeAg 2) HBV DNA Both viral markers were measured quantitatively every month during therapy and every 1-2 months in a follow up of 1 year.		HbsAg (detected by an enzyme immunoassay with a sensitivity of 0.3 ng/ml)	None mentioned.
Results: The authors reported that they have obtained 148 serum samples from the 12 patients who were followed longitudinally during interferon alpha. HbsAg level was significantly correlated with HBV DNA levels during treatment (r=0.76, P<0.001) and HbeAg levels (r=0.70, P<0.001). No difference was found between the prognostic factors in patients with different response patterns (non response n=6, HbeAg seroconversion n=3, HbeAg and HbsAg seroconversion n=3).							

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Baltayiannis 2006	Prospective follow up study of interferon treatment	N=63	HbeAg negative CHB patients who were HbsAg and hepattitis B virus HBV DNA positive at least two occasions 6 months apart, aged 18-71 years, with elevated alanine aminotransferase (ALT) on at least two occasions 3 months prior to	-HBV DNA >10.000 copies/ml measured at 6 months on treatment	6 months during treatment, 12 months (end of treatment), every 12	Relapse during the 6 year follow up (defined as increase of transaminase levels above the normal range and	None.

			their enrollment in the study, and had histological findings of chronic hepatitis (using the scoring system developed by Desmet et al). Patients with HIV, HCV, HDV co infection, cirrhosis or HCC were excluded. Baseline characteristics / Total sample (N=63) Age (yrs), mean (SD) / 51.3 (14.2) Gender (male) / 40/63 Transfusion (n,%) / 6 (9.5) Alcohol (n,%/age) / 14 (22%)/57.8 (9.7) AST (IU/L), median (range) / 130.3 (60-770) ALT (IU/L), median (range) / 177.7 (64-850) Serum HBV DNA (copies/ml), median (range) / 1.2x106 +-5.4 x106 Histological grade, mean+- (range) / 9.6 +-3.7 (2-18) Histological stage, mean+- SD (range) / 2.2 +-1.0 (0-4)		months after the end of treatment for 6 years.	detectable HBV DNA levels at the end of treatment or when responses were not maintained for 6-12 months follow up with the presence of HbsAg (non sustained relapse).	

Results:

	Response evaluation during treatment			
HBV DNA >10.000 copies/ml	BR (biochemical response=	VR (virological response= when	BVR (biochemical and virological	NR (relapse)

	when AST and/or ALT decreased to within the normal range)	serum HBV DNA levels were decreased to undetectable levels by the end of treatment)	response=when AST and/or ALT decreased to within normal range and HBV DNA levels became undetectable at the end of treatment)	
6 months	34/63	22/63	20/63	26/63
12 months	38/63	42/63	36/63	16/63
Follow up	BSR (biochemical sustained response)	VSR (virological sustained response)	BVSR (biological and virological sustained response)	NSR (not sustained response-relapse)
6 months	29/63	30/63	22/63	14/63
12 months	27/63	29/63	21/63	28/63
6 years	12/63			

Factors associated with relapse following interferon-a treatment of patients with hepatitis B e antigen negative chronic hepatitis B by univariate and multivariate analysis

	Univariate analysis		Multivariate analysis*	
	Hazard ratio (95% c.i)	P value	Hazard ratio (95% c.i)	P value
HBV DNA>10,000 copies/ml at 6 months	7.53 (1.73-32.85)	0.007	5.73 (1.16-28.25)	0.032
* Other covariates included age (>45 years), gender, alcohol, ALT at baseline, histological grade and stage.				

Other results: Only alcohol use before recruitment was significantly correlated to relapse in the univariate analysis. HBV DNA levels at 6 months was the only statistical significant predictor of relapse at the multivariate analysis.

Bibliograph	Study type/	Number of	Patient characteristics	Prognostic	Length of	Outcome	Source of

ic reference	Study quality	patients		factor(s)	follow-up	measures	funding
Rijcborst 2010	Investigator-initiated, multicenter, randomized, double blind controlled trial; patients were randomized in 1:! Ratio to receive 180µg of peginterferon alfa-2a weekly and 1000 (body weight<75 kg) or 1200 mg (body weight>=75kg) of ribavirin daily or 180 µg of peginterferon alfa-2a weekly and placebo daily. The duration of therapy was 48 weeks and there was 24 week observation period.	N=133 107/133 had measurements on predictor factors	HbeAg negative patients on two occasions before randomization, positive for HbsAg for more than 6 months, had elevated ALT levels within 2 months before randomization, and had a serum HBV DNA level>100,000 copies/Ml. Exclusion criteria: antiviral or or immunosuppressive therapy within the previous 6 months, coinfection with hepatitis C, D or HIV, other acquired or inherited causes of liver disease, and preexisting cytopenia or decompensated liver disease.	1)HbsAg (with the Architect HbsAg assay (range 0.05-250 IU/ml)) 2)HBV DNA (measured with the TaqMan PCR (lower limit of detection 35 copies/ml-6IU/ml)) Both prognostic factors measured at 4,8, 12,24,36 and 48 weeks of treatment	4, 8, 12, 48 (end of treatment) weeks and at the end of 24 weeks follow up (week 72).	Sustained response (SR) defined as the combined presence of serum HBV DNA levels below 10,000 copies/ml (1714 IU/ml) and normalization of ALT at the end of follow up (week 72) (according to the European Association for the Study of the Liver guidelines, EASL, 2009).	The Foundation of Liver Research (Rotterdam, the Netherlands) was the study initiator and sponsor. F.Hoffmann-La Roche, Ltd (Basel, Switzerland) supplied the drugs and financial support.

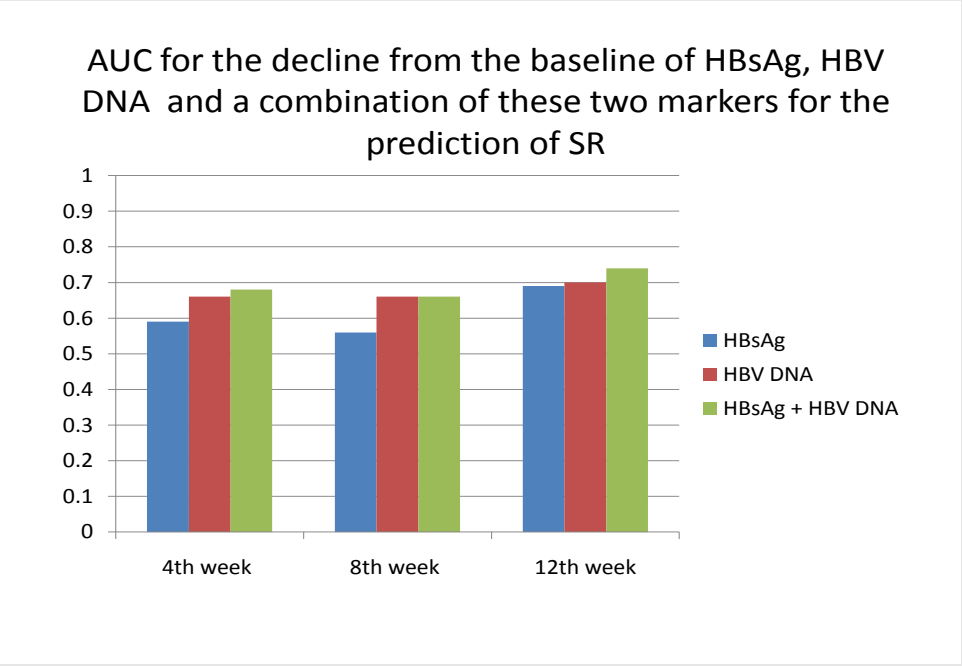
	Patients with SR (N=24)	Patients with no SR (n=83)	P value
Age (yrs), mean (SD)	41 (11)	42 (10)	0.59
Male, n (%)	16 (66.7)	61 (73.5)	0.51
Ethnicity -Caucasian -other	 23(95.8) 1 (4.2)	 79(95.2) 4 (4.8)	0.73
HBV genotype -A -D -other/mixed	 0 23(95.8) 1 (4.2)	 15(18.1) 62(74.7) 6 (7.2)	0.13

ALT, median (IQR)	2 (1.7-3.9)	2.3 (1.6-4.1)	0.82
HBV DNA (copies/ml), mean (SD)	6.9 (1.2)	6.7 (1.2)	0.52
HbsAg,log IU/ml, mean (SD)	3.8 (0.4)	3.8 (0.6)	0.80
Liver necroinflammation, median (IQR)	5 (4- 6)	5 (4-7)	0.52
Liver fibrosis, median (IQR)	2 (1-3)	3 (1-3)	0.57
Cirrhosis, n (%)	0	3 (3.6)	1.0

Results:

24/107 patients (22%) developed SR- the number of sustained responders was comparable between the peginterferon alfa-2a monotherapy group (14/53) and the peginterferon alfa-2a and ribavirin combination group (10/54).

Serum ALT levels behaved similarly in sustained responders and non responders during the treatment phase and were not predictive of SR.

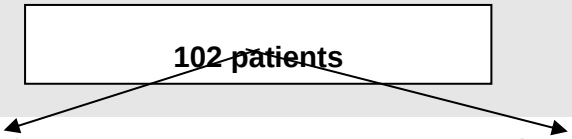


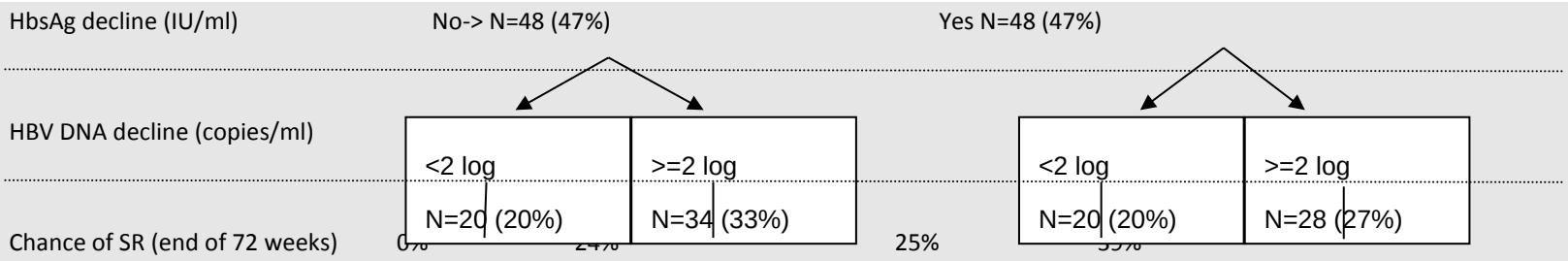
* Figures are taken from graphical presentation so maybe an approximation of the actual values.

HBV DNA declines performed better with respect to the prediction of SR than HbsAg declines at week 4,8 and 12. The best model for fit (which was based on the AUC and AIC), was achieved through a combination of HbsAg and HBV DNA declines (AUC at week 12= 0.74). The performance of the model at week 24 did not improve significantly in comparison with the performance at week 12 (P=0.37). Whether patients were in monotherapy or in combination groups was not associated with SR at any time point (P>=0.35 for all time points).

Based on the previous results, that the combination of markers of HbsAg and HBV DNA declines at week 12 better predicted the SR, the authors identified a stopping rule (cut off point) for discontinuation of therapy in patients who have a very low chance of SR while maintaining more than 95% of sustained responders on treatment.

Week 12





Negative predictive value 100%: none of the patients who didn't have a decline in HbsAg levels and whose HBV DNA levels decreased < 2 log copies/ml (20% of the study population) exhibited a SR.

Patients in who both the virological declines were achieved (and HBV DNA levels decline >=2 log copies/ml) had the highest probability of SR (39%) which was almost double the overall response rate of 22%.

Separate analyses for the treatment groups (monotherapy and combination) resulted in identical cut off values for HbsAg and HBV DNA declines at week 12.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Perillo 1993	Not clearly defined (probably retrospective)	N=29	Consecutive patients positive for HbeAg and HBV DNA before received interferon alpha treatment who had participated in two previous clinical trials in St. Louis. 21 of the treated patients were treated with a 6 week decremental course of prednisone followed by interferon alpha-2 in a dose of 5 MU/day. In all but one individual the IFNa was given for 90 days.	1)HBV DNA (analyzed with a solution hybridization assay- sensitivity was 1/5 ng/lt) 2) HbeAg loss	Week 4th, 8th and 12th during interfeon treatment and at 3 and 6 months after completion of therapy.	Response was defined as the loss of HBV DNA by the end of treatment and the HbeAg loss during a 6-to 9- month posttreatment observation period.	None mentioned.

Results:

16/29 patients were responders

The authors reported that although similar disappearance curves were observed for the two markers (HBV DNA, HbeAg loss) during interferon treatment, HBV DNA became undetectable at an earlier interval in 13 of 16 responders (81%). No futher information was given on the time interval.

Frequency of HbeAg loss monitoring

Predictor		
>90% decrease in HbeAg loss	Responders (N=16)	Non responders (N=13)
At 8 weeks during interferon treatment	11/16 (69%)	0
At 12 weeks during interferon treatment	14/16 (88%)	1/13 (7.7%)

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Fried 2008	Retrospective analysis of a group of patients randomized in a previous trial to receive peginterferon alfa-2a (180µ/ week) plus oral placebo daily for 48 weeks.	N=271 Data on HbeAg were available for 267 patients	HBV infected HbeAg positive patients who have been previously received peginterferon alfa-2a plus oral placebo for 48 weeks. No other information was given in relation to patients baseline characteristics.	1)HbeAg 2)HBV DNA (measured using COBAS AMPLICOR HBV monitor- lower limit of detections was 4 x 102 copies/ml)	Week 12 and 24 during treatment, end of treatment (48 weeks), 24 weeks follow up.	- Response was defined as achievement of HbeAg seroconversion at the end of 72 weeks (48 weeks of treatment and 24 weeks follow up). - Late response was defined as not having achieved HbeAg seroconversion by the end of therapy,	

						but achieved seroconversion by the end of the 24 week follow up.	

Results:

87/271 (32.1%) were responders (achieved HbeAg seroconversion at the end of 24 weeks follow up post treatment-week 72)

HbeAg (PEIU/ml) at 12 weeks during treatment	N, % of responders (HbeAg seroconversion at week 72)
<10	53%
10-100	23%
>100	14%
HBV DNA (log10 copies/ml) at 12 weeks during treatment	
<3	64%
3-5	49%
5-7	29%
>=7	21%

	N, % of responders (HbeAg seroconversion at week 72)	N, % of non responders at week 72
HbeAg (PEIU/ml) at 24 weeks during treatment		
<10 (n=137, 52%)	52% (71/137)	66/137
10-100 (n=54, 21%)	20% (11/54)	43/54
>100 (n=72, 27%)*	4% (3/72)	69/72
HBV DNA (log10 copies/ml) at 24 weeks during treatment		
<5 log copies/ml (n=118, 45%)	53% (62/118)	56/118
5-9 copies/ml (n=89, 34%)	17% (15/89)	74/89
>9 copies/ml (n=56, 21%)**	15% (8/56)	(46/56)

* Specificity=0.92

Negative predictive value=96%

** Specificity=0.72
Negative predictive value=86%

Results also from the receiver operating characteristic curves (to aid the prediction of response at 72 weeks from the predictor factors of HbeAg and HBV DNA at 24 weeks during treatment) showed that HbeAg had greater power (P=0.014) to predict HbeAg seroconversion at week 72 than HBV DNA.

Narrative summary was given for the relationship between HbeAg and HBV DNA levels during treatment and late response (achievement of HbeAg seroconversion at week 72 but not previously seroconverted at the end of 48 weeks of treatment); HBV DNA levels was lower throughout therapy for late responders compared to non responders, however levels reached a plateau during the later few months of therapy, where no further decline in HBV DNA levels occurred despite subsequent HbeAg seroconversion after discontinuation of treatment. HbeAg levels were also consistently lower during therapy in late responders compared with non responders. There was a divergence between HbeAg and HBV DNA dynamics among late responders, with a persistent decrease in HbeAg levels, whereas HBV DNA levels remained relatively flat. The authors believed that tha this reinforces the view that quantitative HbeAg measurements are more predictive of HbeAg seroconversion than HBV DNA levels.

<table>
<tr><th>Bibliographic reference</th><th>Study type/ Study quality</th><th>Number of patients</th><th>Patient characteristics</th><th>Prognostic factor(s)</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Moucari 2009</td><td>Prospective follow up study</td><td>N=48</td><td>HbeAg negative patients with presence of HbsAg in serum for more than 6 months and by liver biopsy showing histological features of chronic hepatitis compatible with HBV infection were treated with pegylated interferon at a dose of 180µg/week for 48 weeks.
Baseline characteristics
<table>
<tr><td></td><td>All patients (N=58)</td><td>SVR (n=12)</td><td>Relapsers n=36)</td><td>P value</td></tr>
<tr><td>Age (years)</td><td>44 (38-53)</td><td>45 (42-54)</td><td>43 (36-53)</td><td>0.2</td></tr>
<tr><td>Sex, %</td><td>83</td><td>83</td><td>83</td><td>1</td></tr>
</table></td><td>1) HBV DNA levels (lower limit of detection 70 copies/ml (1.85 log10 copies/ml)
2) HbsAg levels (0.5log IU/ml and 1 logIU/ml as cut off points)</td><td>Every 4th week during the 48 weeks of treatment, end of treatment and at 24 weeks follow up after end of treatment.</td><td>1)End of treatment response (EOT) was defined as undetectable serum HBV DNA at the end of treatment.
2)Non response was defined as detectable HBV DNA at the EOT.</td><td>None mentioned.</td></tr>
</table>

			male						
			Serum ALT (IU/L)	98 (60-240)	220 (120-390)	90 (54-172)	0.006		
			HBV DNA (log copies/ml)	7.0 (5.5-8.0)	8.0 (6.1-8.8)	6.8 (5.5-8.0)	0.1		
			HbsAg (log IU/ml)	3.8 (3.2-4.2)	3.9(2.9-4.3)	3.8 (3.2-4.1)	0.8		
			Liver necroinflammation, % A2-A3	50	50	50	1.0		
			Liver fibrosis, % F3-F4	50	50	50	1.0		

3)Sustained virological response (SVR) was defined as undetectable serum HBV DNA at 24 weeks after end of treatment.

4)Relapse was defined as undetectable HBV DNA at the end of treatment and a subsequent detectable serum HBV DNA within the 24 weeks after treatment cessation.

Results:

30 patients (62%) showed and EOT response, and 18 (38%) were non responders

12 patients (25%) achieved SVR while 18 patients relapsed (end of 24 weeks follow up after the end of treatment)

Prognostic factor: HBV DNA levels during interferon treatment

	Responders (end of 48 weeks of interferon treatment) (n=30)	Non responders (end of 48 weeks of interferon treatment) (n=18)	P value
Mean decrease in HBV DNA in the first 12 weeks of treatment (SD) in log10 copies/ml	4.1 (1.9)	2.2 (1.7)	0.01
Mean decrease in HBV DNA in the first 24 weeks of treatment (SD) in log10	5.1 (1.9)	2.2 (2.3)	0.002

copies/ml			

	Patients with SVR (end of 24 weeks after the end of treatment) (n=12)	Patients with no SVR (end of 24 weeks after the end of treatment) (n=36)	P value
Decrease in HBV DNA in the first 12 weeks of treatment (mean, SD) in log10 copies/ml	4.1 (1.9)	3.0 (1.7)	0.1
Decrease in HBV DNA in the first 24weeks of treatment (mean, SD) in log10 copies/ml	5.1 (1.9)	4.2 (1.4)	0.2

The authors reported that during interferon treatment, patients who developed SVR showed a marked decrease in serum HbsAg, with mean decreases of 0.8 (0.5), 1.5 (0.6), 2.1 (1.2) log10 copies/ml at 12, 24 and 48 weeks respectively but only reported narratively that HbsAg levels did not decrease during treatment in patients who failed to achieve SVR.

Predictive value of serum HbsAg on SVR

	Patients with SVR (end of 24 weeks after the end of treatment) (n=12)	Patients with no SVR (end of 24 weeks after the end of treatment) (n=36)	Positive predictive value (PPV)/ negative predictive Value (NPV)/area under the curve (AUC)
At 12 weeks during interferon treatment			
HbsAg >=0.5 log10 IU/ml	8 (66.6%)	1	PPV= 89%, NPV= 90%
HbsAg <0.5 log10 IU/ml	4	35 (97.2%)	
At 24 weeks during interferon treatment			
HbsAg >=1 log10 IU/ml	11 (91.6%)	1	PPV= 92%, NPV= 97%, AUC= 0.944
HbsAg <1 log10 IU/ml	1	35 (97.2%)	

The authors concluded that early serum HbsAg drop has high predictive value of SVR to pegylated interferon in HbeAg negative CHB patients and that HbsAg may be a useful tool to optimize the management of pegylated interferon in these patients.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Rijckborst et al, 2012. Validation of a stopping rule at week 12 using HBsAg and HBV DNA for HBeAg negative patients treated with pginterferon alfa-2a	Retrospective analysis of three trials (PARC (pegylated IFN a-2a +/- ribavirin for 48 weeks), phase III trial (pegylated IFN a-2a for 48 weeks), PegBeliver study (pegylated IFN a-2a for 96 weeks))	N (PARC)=102, N (phase III trial)=85, N(PegBeliver study)=75	HbeAg negative patients with presence of HbsAg in serum for more than 6 months and elevated ALT between 1 and 10 times the ULN and had serum HBV DNA level exceeding 100,000 copies/ml. Exclusion criteria: antiviral treatment 6 months prior to randomization, viral co-infection (HCV, HDV or HIV) and decompensated liver disease. Patients were treated in three trials (PARC (pegylated IFN a-2a +/- ribavirin for 48 weeks), phase III trial (pegylated IFN a-2a for 48 weeks), PegBeliver study (pegylated IFN a-2a for 96 weeks)) Baseline characteristics PARC (n=102) / Phase III trial (n=85) / PegBeLiver (n=75) Mean (SD) age, years: 41 (10) / 41 (10) / 44 (10) Sex, n (%) male: 74 (72.5%) / 70 (82.4%) / 55 (73.3%) Ethnicity (%) Caucasian: 97(95.1) / 30(35.3) / 75(100) Asian: 3(2.9) / 52(61.2) / 0 Other: 2(2.0) / 3(3.5) / 0	Any HBsAg decline and/or >=2log HBV DNA decline at 12 weeks during pegylated IFN a-2a treatment	24 weeks post treatment	Sustained response: combined presence of serum HBV DNA<2000 IU/ml and normal ALT after 24 weeks of post-treatment	Foundation for Liver and Gastrointestinal Research, Rotterdam, the Netherlands.

			Genotype (%) A B C D	 14(13.7) 0 2(2.0) 81(79.4)	 8(9.4) 18(21.2) 34(40.0) 21(24.7)	 2(2.7) 0 0 70(93.3)				
			Mean (SD) ALT	3.2 (2.5)	3.1 (2.8)	3.2 (2.8)				
			Mean (SD) HBV DNA, log IU/ml	6 (1.2)	6.7 (1.9)	6.2 (1.4)				
			Mean (SD) HBsAg, log IU/ml	3.8 (0.6)	3.4 (0.6)	3.7 (0.4)				
			Cirrhosis (%)	3 (2.9)	7 (8.2)	5 (6.7)				

Results:

	PARC	**Trial III**	**PegBeLiver Study**
Sustained response (HBV DNA<2000 IU/ml and ALT normal 24 weeks after treatment) (%)	25/102 (25)	32/85 (38)	25/75 (33)
Mean (SD) HBsAg decline at week 48	Responders : 1.26 (1.43) log Non responders : 0.24 (0.59) log	Responders : 1.15 (1.37) log Non responders : 0.38 (0.66) log	48 week arm: Responders : 0.64 (1.26) log Non responders : 0.17 (0.37) log 96 week arm: Responders : 1.04 (1.11) log Non responders : 0.05 (0.44) log
HBV DNA decline during treatment	Same observation across three studies: the degree of HBV DNA decline was stronger in patients who had sustained response, although HBV DNA levels decreased considerably in those without a SR.		

Validation of stopping rule: none of the PACR participants without a decrease in HBsAg and with less than 2log HBV DNA decline at week 12 achieved a SR (NPV 100%)

Despite the different baseline characteristics, the stopping rule performed well across the three trials. In the validation trials only 5% of the patients without a decrease in HBsAg and with less than 2 log HBV DNA decline at week 12 had a SR (NPV 95%).

20% of patients in PACR study had HBsAg decline but not HBV DNA decline>= 2 log and would be allowed to discontinue therapy at week 12 while keeping all responders to treatment ,compared with only 14% in the validation trials.

When results were repeated only for those infected with HBV genotype D, the performance of stopping rule was similar in all trials.

Performance of stopping rule for patients treated with pegylated IFN for 96 weeks; none of the seven patient (21%) without a decrease in HBsAg and with less than 2 log HBV DNA decline at week 12 achieved a SR

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Piratvisuth et al, 2011. Hepatitis B surface antigen: association with sustained response to peginterferon alfa-2a in hepatitis B e antigen-positive patients	Retrospective analysis of a randomized trial of peginterferon alfa-2a alone or in combination with lamivudine for 48 weeks	N=399	HbeAg positive patients treated with peginterferon alfa-2a alone (n=204) or in combination with lamivudine (n=195) and with HBsAg values available at all time points (baseline, weeks 12, 24, 48 and 72). The majority of patients were infected with HBV genotype B (32.6%) or genotype C (58.4%). Baseline characteristics Overall population (n=542) / In this analysis (n=399) Age (years), mean (SD): 32.1 (9.97) / 31.8 (9.62) Sex, n (%) male/female: 77.9/22.1 / 75.4/24.6 Ethnicity (%) Caucasian/oriental/other: 8.7/87.8/3.5 / 5.5/91.5/3.0	HBsAg levels at baseline, at 12 and 24 weeks during treatment (quantified using the ABBOTT Architect HBsAg assay)	6 months	1) HbeAg seroconversion 6 months after treatment 2) HBV DNA<=2,000 IU/ml 6 months post treatment 3) HBsAg clearance 6 months post treatment	Research grant was provided by F.Hoffmann-La Roche, Basel, Switzerland.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics			Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
			Genotype (%) A/B/C/D	7.6/29.2/58.7/3.7	5.8/32.6/58.4/2.5				
			HBV DNA (log 10 x copies/ml) mean (SD)	10 (1.99)	10 (1.97)				
			HBsAg (log10 IU/ml Mean (SD)	4.1 (0.68)	4.1 (0.67)				
			ALT (IU/L) Mean (SD)	114.8 (104.59)	119.6 (107.89)				

Results:

Outcomes at 6 months post treatment: HBeAg seroconversion 34% (137/399), HBV DNA <=2000 IU/ml 28% (112/399), HBsAg clearance 4% (17/399)

	Outcome: HBeAg seroconversion at 6 months post treatment		
Prognostic factor	Responders	Non responders	P value
HBsAg levels at baseline, mean (SD) (were similar for both treatment groups and results were grouped)	3.97 (0.72) log 10 IU/ml	4.21 (0.63) log 10 IU/ml	0.039

- Results of ROC analysis showed that a lower level of HBsAg at 5,000 IU/ml at baseline resulted in a positive predictive value (PPV) for HBeAg seroconversion at 6 months post treatment of 42% and a NPV of 68%. Applying an upper cut off at baseline of 50,000 the NPV increased to 77%.
- HBsAg decline was significantly higher at weeks 12, 24 during treatment, 48 (end of treatment) and 72 (follow up) in patients with HBeAg seroconversion 6 months post treatment than in patients without HBeAg seroconversion (p=0.036, <0.0001, <0.0001 and <0.0001 respectively).
- HBV DNA decline was significantly higher at all on treatment (12, 24 weeks) and post treatment point times (48 and 72 weeks) in

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding

responders to peginterferon alfa-2a monotherapy compared to non responders. However, in the combination group of peginterferon a-2a plus lamivudine, a significant difference between responders and non responders was observed only at 72 weeks.

- ROC analysis identified the level of HBsA<1,500 IU/ml at weeks 12 and 24 that generated PPV of 55% for HBeAg seroconversion at 6 months post treatment (57% for 12 weeks and 54% for 24 weeks). When a cut off point of HBsAg levels of 20,000 IU/ml was introduced, the NPVs increased to 84% and 85% respectively.
- For all patients treated with peginterferon alfa-2a alone or in combination with lamivudine; 22.6% had HBsAg levels<1,500 IU/ml at 12 weeks and this increased to 34.1% at week 24.
- For patients who achieved HBeAg seroconversion at 6 months post treatment;

	12 weeks	24 weeks
HBsAg levels<1,500 IU/ml	56.7%	56.4%
HBsAg levels 1,500-20,000 IU/ml	32.3%	26.1%
HBsAg levels >20,000 IU/ml	16.3%	15.4%

- Higher rates of HBsAg clearance 6 months post treatment were also achieved by patients with HBsAg <1,500 at weeks 12 and HBeAg seroconversion at 6 months post treatment (17.6%)
- For patients with Genotype B; HBeAg seroconversion at 6 months post treatment was achieved by 50% and 50% of patients with HBsAg <1,500 IU/ml at weeks 12 and 24. These proportions for patients with Genotype C were 59% and 55% respectively.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Marcellin et al, 2012. Hepatitis B surface	Long term follow up study/	N (follow up study)=2	HBeAg negative patients received peginterferon alfa-2a (180µg/week)+/- lamivudine (100mg/day) for 48 weeks as part of the large, multicentre, randomized	HBsAg levels at 12 and 24 weeks	5 years/retrospective	Efficacy: 1) HBV DNA<=2,000 IU/ml	By a research grant from

<table>
<tr><th>Bibliographic reference</th><th>Study type/ Study quality</th><th>Number of patients</th><th>Patient characteristics</th><th>Prognostic factor(s)</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>antigen levels: association with 5-year response to peginterferon alfa-2a in hepatitis B e-antigen-negative patients.</td><td>retrospective analysis (only for those with HBsAg values available at each time point)</td><td>30/ N (retrospective analysis) =120</td><td>Phase 3 study (Marcellin, 2009).
Baseline characteristics
<table>
<tr><th></th><th>Long term follow up (n=230)</th><th>Long term follow up with available HBsAg at all time points (n=120)</th></tr>
<tr><td>Ethnicity (%)
Caucasian/Asian/other</td><td>27/72/1</td><td>32/67/2</td></tr>
<tr><td>Sex, n (%) male/female</td><td>83/17</td><td>375/25</td></tr>
<tr><td>Genotype (%)
A/B/C/D</td><td>7/28/42/20</td><td>10/20/46/22</td></tr>
<tr><td>Age (years) mean (SD)</td><td>39.9(11)</td><td>41.3 (9.9)</td></tr>
<tr><td>HBsAg (log10 IU/ml), mean (SD)</td><td>3.39 (0.61)</td><td>3.40 (0.61)</td></tr>
<tr><td>HBV DNA (log10 IU/ml), mean (SD)</td><td>6.46 (1.91)</td><td>6.49 (1.85)</td></tr>
<tr><td>ALT (IU/L) mean (SD)</td><td>87 (75)</td><td>92 (87)</td></tr>
</table></td><td></td><td>analysis</td><td>(=10,000 copies/ml)

2) HBsAg clearance at 1 and 5 years post treatment</td><td>F.Hoffmann-La Roche, Basel, Switzerland.</td></tr>
<tr><td colspan="8">Results:
Data from HBsAg decline were pooled for both treatment groups (peginterferon alfa-2a monotherapy and combination plus lamivudine), whereas HBV DNA decline has been shown to be greater in patients with peginterferon alfa-2a plus lamivudine compared to monotherapy, thus results were analysed individually.
<table>
<tr><th></th><th>Long term follow up study (n=230)</th><th>Long term follow up population with HBsAg available at all time points (n=120)</th></tr>
</table></td></tr>
</table>

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding

Response at 1 year post treatment, n(%)		
HBV DNA<=2000 IU/ml	72 (31)	36 (30)
HBsAg clearance	11 (5)	6 (5)
Response at 5 year post treatment, n(%)		
HBV DNA<=2000 IU/ml	54 (23)	31 (26)
HBsAg clearance	28 (12)	17 (14)

- In patients with available data at years 1 and 5 post treatment, 88% (36/41) sustained suppression of HBV DNA<=2,000 IU/ml. The rate of HBsAg clcearance at 5 years post-treatment was significantly higher in patients with HBV DNA<=2,000 IU/ml at 1 year post treatment (20/72, 28%) than in patients with HBV DNA>2,000 IU/ml at 1 year post treatment (8/158, p<0.0001).
- Baseline HBsAg as a predictors of response: Receiver Operating Characteristic (ROC) analysis identified baseline HBsAg level of 5,000IU/ml was associated with a positive predictive value (PPV) of 34% and 30% for HBV DNA <=2,000 IU/ml at 1 and 5 years post treatment respectively. The negative predictive values were 78% and 84% respectively.
- HBsAg decline during treatment: HBsAg decline during treatment (48 weeks) and the initial follow up period (24 weeks) was significantly more pronounced in patients with HBsAg clearance at either 1 or 5 years post-treatment when compared with patients not achieving HBsAg clearance or HBV DNA suppression.
- HBsAg clearance was more pronounced in virological responders (achieved HBV DNA<=2,000 IU/ml at the end of treatment and 5 years post-treatment) (55%) than in relapsers (achieved HBV DNA<=2,000 IU/ml at the end of treatment but not at 5 years post-treatment) and non responders (not achieved HBV DNA<=2,000 IU/ml at any point at post-treatment)
- HBsAg decline during treatment as predictor of response: ROC analysis identified >=10% log10 HBsAg decline from baseline was associated with post treatment response. Patients with >=10% log10 HBsAg decline from baseline achieved significantly higher rates of HBV DNA<=2000 IU/ml at both year 1 and 5 post treatment than patient with <10% log10 HBsAg decline.

Predictor: HBsAg decline from baseline to week 12>=10%log10			
	HBV DNA<=2,000 IU/ml at year 1	HBV DNA<=2,000 IU/ml at year 5	HBsAg clearance at year 5
PPVs	47%	42%	23%

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding

NPVs	84%	87%	93%

Predictor: HBsAg decline from baseline to week 24>=10%log10			
	HBV DNA<=2,000 IU/ml at year 1	HBV DNA<=2,000 IU/ml at year 5	HBsAg clearance at year 5
PPVs	43%	36%	22%
NPVs	87%	87%	96%

- 40% of patients with >=10% HBsAg decline from baseline at week 12 and HBV DNA<2,000 IU/ml at 1 year post treatment had HBsAg clearance at 5 years post treatment whereas this proportion came to 44.8% for those with >=10%HBsAg decline from baseline at week 24.

E.7.4 Patients with CHB on nucleos(t)ides treatment

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Jaroszewicz 2011	Prospective cohort	N= 126	Recruitment/setting: university hospital between 1998 and 2008. Inclusion: patients underwent NA treatment who achieved HBV DNA suppression <100IU/mL (VR) during follow up without occurrence of virological breakthrough. Exclusion: HDV, HCV, HIV infection. Baseline characteristics (N=95*) Median age, years (range): 46 (28-64) Male/female, n: 74/21 Median HBV DNA, log10 IU/mL (10-90% CI): 5.74 (3.53-8.04) Median HBsAg, log10 IU/mL (10-90% CI): 3.78 (2.85-4.79) Median ALT (U/L), IU/mL (10- : 80 (33-496)	HBsAg quantified at multiple time points (baseline 6 months after start of treatment, at first time point of VR and on a yearly basis thereafter. Early decrease: between baseline and 6 months; late decrease: during 2 years reaching VR.	6-107 months	1. HBsAg loss	Not stated.

			90% CI)		HBsAg was measured using Abbott Architect assay (dynamic range: 0.05-250 IU/mL)		
			HBeAg positive, n (%)	31 (33)			
			HBV genotype (%) A D Other Not determined	 20(21) 47 (49) 13 (14) 15 (16)			
			Previous NA treatment Lamivudine Entecavir Adefovir Tenofovir Other treatments	 29 24 12 9 2			
			*6 experienced HBsAg loss, 89 with persistent HBsAg levels.				

Results:

Median HBsAg decrease was 0.81 log10 from baseline to 3 years after patients achieved VR.

42% patients with a strong HBsAg decrease 2 years after VR cleared HBsAg.

All patients without strong HBsAg decrease (>0.5 log10) 2 years after VR did not clear HBsAg.

Early HBsAg decrease after 6 months of NA therapy was not associated with HBsAg loss.

HBsAg kinetics did not differ significantly between different NA treatments. The number of patients in some of the treatment regimen was small, hence did not allow for an adequate comparison of all NA drugs.

6 (6.3%) patients lost HBsAg after median duration of 40 months (range 17-107) of continuous NA treatment.

Early HBsAg decrease during first 6 months during therapy (n=95)

	%	Median HBsAg decrease
>0.5 log 10 IU/mL strong decrease	25	1.00 log10
10% - 0.5 log 10 IU/mL moderate decrease	44	0.21 log10

<10% no decrease	31	-0.10 log10

Early decrease of HBsAg 6 months after start of therapy does not correlate with late HBsAg decrease and later HBsAg loss.

Late HBsAg decrease 2 years after virologic response (with continuous HBV DNA suppression <100IU/mL) during NA therapy (n=64)

Level of HBsAg decrease during 2 years	n(%)	Median HBsAg decrease
>0.5 log 10 IU/mL decrease	12 (19%)	0.84 log10
10% - 0.5 log 10 IU/mL decrease	34 (53%)	0.21 log10
<10% decrease from baseline	18 (28%)	-0.05 log10

Late HBsAg decrease during 2 years after VR was associated with HBsAg loss.

Author's conclusion: HBsAg decrease during NA treatment is generally weak and HBsAg decrease during the first 6 months of NA therapy was not predictive for HBsAg loss. HBsAg suppression is a rare event during NA therapy. Monitoring qHBsAg after successful HBV DNA suppression might be useful to identify patients who clear HBsAg, implicating finite NA treatment.

E.7.5 Patients with CHB on lamivudine treatment

Reference	Study type	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding	
Franca 2007	Prospective cohort Small sample size	N= 28	Recruitment/setting: 4 Brazilian regional reference centres for chronic hepatitis treatment Inclusion: all presented clinical or biochemical signs of chronic active hepatitis. On first time LAM treatment, 150mg orally once daily Exclusion: none were HIV and/or HCV carriers Baseline characteristics Men, n (%) 24 (86) Women, n (%) 4 (14)	Resistance - YMDD mutants using INNO-LiPA (line probe assay) Monitored	12-18 months	Biochemical flare, defined as an increase in ALT > 3 x ULN from normal levels in the preceding samples.	Not stated.	

			Ethnicity (%) Caucasian Black Asian Age, mean ±SD (range) HBeAg positive, n Anti-HBe antibodies, n ALT, n (%) Higher than normal >2 x ULN HBV genotype, n (%) A D C F	 75 18 7 44 ± 12 (22-65) 12 16 22 (79) 13 (46) 19 (68) 6 (21) 2 (7) 1 (4)	monthly		HBV DNA was isolated using partial genome amplification by qualitative nested PCR (lower detection limit of 500 copies/mL)		

Table 1. Biochemical and virologic response rates after 6, 12 and 18 months of lamivudine therapy

	% of people (n/N)		
Response	6 months	12 months	18 months
Biochemical Normal ALT level ALT breakthrough	 82%(22/27) -	 82% (23/28) 7% (2/28)	 53% (9/17) 12% (2/17)
Virologic Undetectable HBVDNA HBV DNA breakthrough	 57% (16/28) -	 68% (19/28) 14% (4/28)	 53% (9/17) 29% (5/17)
Biochemical + virologic			

Normal ALT level and undetectable HBV DNA	48% (13/28)	75% (21/28)	53% (9/17)
Mean ALT levels (SD) (Pretreatment ALT: 4.62 ± 7.27)	0.83 ± 0.40	1.45 ± 0.39	1.04 ± 0.47

Monitoring LAM resistance (YMDD variant and concomitant rtL180M)

One or more of these mutations were identified in 8 (29%) of the 28 patients who received LAM for at least 1 year.

All 8 viral breakthrough cases were related to the emergence of YMDD variants observed in 7, 21, and 35% of patients at 6, 12 and 18 months, respectively.

The occurrence of viral breakthrough was only observed in patients with detectable YMDD variants.

The emergence of YMDD variants was also associated with biochemical relapse.

The identification of variants associated with LAM resistance was significantly earlier (41±14 weeks) than the subsequent ALT relapse (60±15 weeks) in the same patients. The time lag between detection of YMDD variants and the emergence of biochemical breakthrough during LAM therapy was 19± 2 weeks.

Table 2. Virologic and biochemical findings among YMDD variants carriers

Patients	Age (years)	HBV genotype	YMDD variants		Virologic follow up		Biochemical follow up		
			Mutation	Detection (wk)	Undetectable HBV DNA (wk)	Breakthrough (wk)	ALT normalisation (wk)	Breakthrough (wk)	Peak of AL elevation
1	65	A	rtM204V rtL180M	44 44	26	44	N/A	63	3.3
2	44	A	rtM204V rtL180M	33 33	Not observed		Not observed		
3	38	A	rtM204V rtL180M	34 34	8	34	12	51	19.2
4	45	A	rtM204I	43	25	43	9	64	5.4
5	55	A	rtM204I	62	49	55	N/A	82	3.3
6	36	A	rtM204V rtL180M	23 33	Not observed		11	41	5.3
7	32	A	rtM204I rtM204V	23 53	34	53	40		

			rtL180M	53					
8	48	D	rtM204I	45	Not observed		19	Unknown	

Author's conclusion: The detection of resistance-associated mutations was observed before the corresponding biochemical flare in the same individuals. If highly sensitive LAM drug resistance testing is carried out at frequent and regular intervals, the relatively long period between the emergence of viral resistance and the onset of biochemical relapse can provide clinicians with ample time to re-evaluate drug therapy. The frequent monthly sampling done in the present study allowed early detection of the emergence of LAM resistant strains.

Reference	Study type	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding	
Llop 2009	Retrospective study Small sample size Two groups of treatment were analysed independently.	N= 66 On LAM (n=31) or ADV (n=35) treatment	Recruitment/setting: Clinical records reviewed retrospectively. University hospital, Spain Inclusion: CHB patients treated with LAM or ADV between 2001 and 2006. Exclusion: people with cirrhosis or hepatocellular carcinoma on antiviral therapy. Baseline characteristics	Viral DNA measured at month 1, 3 and 6	N/A	Virologic response – defined as undetectable HBV DNA (<200 copies) Biochemical response – defined as normalisation of ALT (ULN 40 IU/L)	Not stated.	

	LAM (n=31)	ADV (n=35)
Age at treatment onset (years), mean (SD)	38 (12)	42 (14)
Sex, n Male:female	 24:7	 31:4
Transmission,n Transfusion Sexual Perinatal	 6 1 3	 4 4 2

Surgery	1 / 1
Surgery	20 / 24
HBeAg, n	
Positive	10 / 11
Negative	21 / 24
Previous treatment,n	
IFN or peg IFN	10 / 2
LAM	0 / 24

Results

Table 1. Differences in pattern of viral load decrease in responders vs. nonresponders (virologic response at 1 year) to LAM and ADV

Prognostic factors	Weeks	LAM		ADV	
		Responders	Non responders	Responders	Non responders
Mean viral load decrease (in log)	4	1.2 (1.8)	2.7 (1.3)	1.6 (1.1)	0.8 (1.4)
	12	2.7 (0.99)	2.7 (1.5)	2.4 (1.1)	1.3 (1.3)
	24	2.8 (1.2)	3.5 (1.3)	2.6 (1.2)	1.3 (1.2)
Mean viral load decrease from baseline (%)	4	19.5 (26.3)	33.5 (13.6)	32.1 (17.6)	11 (21.9)
	12	49.2 (13.2)	38.3 (20.4)	46.6 (13.9)	19.9 (20)
	24	52.1 (14.5)	50.8 (15.4)	49.3 (12.7)	21.1 (19.8)

Table 2.ROC curves (AUC) at week 12 from treatment onset with lamivudine

	AUC
Viral load decrease from baseline (%)	0.675

A % of viral load decrease from baseline ≤30% had a sensitivity of 92% and a negative predictive value of 80%.

Table 3. ROC curves (AUC) at week 12 and 24 from treatment onset with adefovir

Adefovir	AUC
Viral load decrease from baseline (%) Week 12 Week24	 0.83 0.9
Decrease in log viral load Week 12 Week 24	 0.77 0.79

At week 24 a decrease in viral load of 1 log had 93% sensitivity and 80% negative predictive value

A % of viral load decrease from baseline ≤20% had 100% sensitivity and 100% negative predictive value.

AUC = Area under the ROC curve, or c statistics, ranges from 0.5 (no discrimination) to a theoretical maximum of 1 (perfect discrimination).

ROC curve = A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 – specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.

Author's conclusion: The decrease in viral DNA at weeks 12 and 24 can predict virologic response at 1 year in patients with CHB treated with LAM or ADV.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Kim 2007A	Prospective cohort study No details of recruitment method or setting	N= 221 (180 HBeAg positive; 41 HBeAg negative)	Recruitment/setting: Korea Inclusion: CHB patients underwent lamivudine therapy for >6 months. Exclusion: No history of antiviral treatment. Additional drug use such as immunosuppressant agents or chemotherapeutic agents Baseline characteristics Group 1*: Mean age, years (SD): 41.1 ±11.2 Group 2*: Mean age, years (SD): 43.7±8.9	Serum HBV DNA HBeAg Anti-HBe ALT Monitor every 2-3 months during lamivudine therapy	Up to 2 years	1.Viral breakthrough Group 1 - reversion of serum HBV DNA to detectable levels during LAM therapy Group 2 – rebound of serum HBV DNA to a level greater than 1 log10 of the lowest level recorded during LAM therapy	Not stated

			Male/female: 163/41; 14/3 HBV DNA (log 10 copies/mL), mean ±SD: 7.82±0.84; 8.15±0.87 ALT (IU/L), mean ±SD: 377±351; 223±102 HBeAg (+) (-): 165/39; 15/2 Cirrhosis (yes/no): 84/120; 5/12 Duration of LAM (weeks), mean ±SD: 93.9±61; 80.5±55 *Group 1, patients whose serum HBV DNA became undetectable during the initial 6 months after initiation of LAM therapy (n=204). Group 2, patients whose serum HBV DNA levels were persistently detectable during the initial 6 months after initiation of LAM therapy (n=17).	Serum HBsAg, HBeAg and anti-HBe were measured using an immunoradiometric assay kit Serum HBV DNA measured using a solution-hybridisation assay kit (lower limit of detection 2.83 x 105 copies/mL)		2.HBeAg loss 3.ALT normalisation	

Results:

Of 221 patients, 31 had persistently detectable levels of serum HBV DNA during the first 3 months after start of LAM therapy. 14/31 became HBV DNA undetectable between 3 and 6 months. 17/221 had persistently detectable HBV DNA at 6 months after start of LAM therapy.

	Group 1 (undetectable HBV DNA) (n=204)	Group 2 (persistently detectable HBV DNA) (n=17)	P value
Cumulative rate of viral breakthrough 12 months after LAM initiation	43 (21%)	11 (63%)	P<0.001
Cumulative rate of HBeAg loss 12 months after LAM initiation 24 months after LAM initiation	78 (38%) 124 (61%)	0 (0) 0 (0)	P<0.001
Rate of ALT normalisation 6 months after LAM initiation	161 (79%)	8 (47%)	P=0.003

12 months after LAM initiation	145 (71%)	5 (28%)	P=0.001

Author's conclusion: Lamivudine had little effect on serum HBV DNA suppression, viral breakthrough suppression and rate of HBeAg loss and ALT normalisation in chronic hepatitis B patients with persistently detectable serum HBV DNA during the initial 6 months of therapy. Early termination of lamivudine therapy is advocated for these patients.

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of patients</th><th>Patient characteristics</th><th>Prognostic factor(s)</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Chan 2011</td><td>Retrospective study

Small sample size</td><td>N= 53
59 were excluded (44 discontinued LAM, 5 died or developed HCC within one year, 1 patient had LAM <1 year and 9 were followed up with no outcome data available.</td><td>Recruitment/setting: China
Inclusion: HBeAg negative CHB patients who had continuous treatment with lamivudine for at least 12 months and had post-treatment follow up for at least 12 months. No patients had exposure to pegylated interferon or to any other nucleos(t)ides.
Exclusion: coinfection with HCV
Baseline characteristics
<table>
<tr><th></th><th>All (n=53)</th><th>Responder (n=9)</th><th>Non-responder(n=44)</th></tr>
<tr><td>Male gender, n (%)</td><td>43 (81)</td><td>7 (78)</td><td>36 (82)</td></tr>
<tr><td>Age, years</td><td>56 (10)</td><td>48 (15)</td><td>46 (9)</td></tr>
<tr><td>ALT (IU/L)</td><td>117 (15-5430)</td><td>114 (15-1800)</td><td>117 (33-2379)</td></tr>
<tr><td>HBV DNA, log IU/ml</td><td>5.8 (1.4)</td><td>5.7 (2.0)</td><td>5.9 (1.3)</td></tr>
<tr><td>HBsAg, log IU/ml</td><td>3.2 (0.8)</td><td>2.9 (1.4)</td><td>3.3 (0.6)</td></tr>
</table></td><td>Quantitative HBsAg at baseline, month 6, and at the end of LAM treatment
Architect HBsg QT (Abbott Diagnostics)</td><td>12 months post-treatment</td><td>Sustained response, defined as HBV DNA ≤200 IU/ml, at 12 months post-treatment.</td><td>Research und for the Control of Infectious Diseases grant</td></tr>
</table>

			HBV genotype B:C	24:29	5:4	19:25		
			Treatment duration, months	27 (15)	34 (23)	26 (13)		
			No difference in baseline characteristics was found between the two groups of patients.					

Results

Patients had received LAM for 34 (SD23; range 12-76) months

Predictors of sustained response at month 12 post-treatment

	Responders	Non-responders	P value
HBV DNA			
Month 6	2.2 (0.9)	2.4 (1.1)	0.68
Month 12	2.0 (0.7)	2.5 (1.6)	0.56
HBsAg (log IU/ml)			
Baseline	2.9 (1.4)	3.3 (0.6)	0.38
Month 6	2.1 (1.1)	3.2 (0.5)	0.001
Month 12	0.8 (1.7)	3.1 (0.6)	<0.001
Reduction of HBsAg from baseline			
Month 6	0.8 (1.0)	0.03 (0.40)	<0.001
Month 12 (end of treatment)	2.1 (1.7)	0.2 (0.5)	<0.001

ROC curves for HBsAg at month 6 and 12

	Area under ROC curve (95% CI)	P value
Month 6		
Absolute HBsAg level	0.84 (0.69-0.99)	0.001
Reduction in HBsAg level	0.75 (0.55-0.94)	0.011

Absolute HBV DNA	0.46 (0.26-0.66)	0.69
Reduction in HBV DNA	0.52 (0.31-0.73)	0.83
End of treatment		
Absolute HBsAg level	0.91 (0.78-1.00)	<0.001
Reduction in HBsAg level	0.96 (0.89-1.00)	<0.001
Absolute HBV DNA	0.44 (0.24-0.63)	0.55
Reduction in HBV DNA	0.51 (0.27-0.72)	0.96

The AUCs were generally greater at the end of treatment than that at month 6, indicating that measurement of HBsAg at the end of treatment was more accurate than at month 6 to predict sustained response 12 months post treatment.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Wang 2010A	Prospective cohort study	N= 125	Recruitment/setting: China Inclusion: HBeAg positive patients. Seropositive for HBsAg and HBeAg for more than 6 months before treatment and had no signs of decompensated liver disease. ALT no less than 2 x ULN (or 40 IU/L) and serum HBV DNA levels at least 105 copies/mL when initiating treatment in all patients. A 6-month combination with IFN alpha at initiation of LAM were given in 62 patients and none of other NAs were added throughout the treatment. Patients needed to meet the cessation criterion. AASLD cessation criterion: receiving ≥ 6 month additional lamivudine treatment after achieving HBeAg seroconversion/loss with undetectable HBV DNA by PCR assay and normal ALT plus an at least 12 month total treatment duration for patients who	1.HBV DNA*, measured by real-time quantitative PCR assay, lower limit of detection 1x103 copies/mL) Evaluated monthly in the 1st 4 months after cessation and at months 6,9, and 12 and thereafter at 6 month intervals	Median 24 (2-84 months)	1. cumulative relapse, defined as reappearance of serum HBV DNA ≥104 copies/mL, by PCR assay with/without reappearance of HBeAg	Not stated.

underwent HBeAg seroconversion or an at least 18 month total treatment duration for those who underwent HBeAg loss.

Exclusion: see above.

Baseline characteristics

	Group A*	Group B*
Number	82	43
Mean age, years (SD)	25.8 ± 12.6	31.7 ± 10.7
Male/female	64/18	31/12
HBV DNA (log 10 copies/mL), mean ±SD	7.26±1.02	7.21±0.82
ALT (IU/L), median (range)	218 (81-1867)	242.5 (80-1055)
Combination with IFN, n	40	22
Time to HBeAg seroconversion or loss (months), median (range)	6 (1-48)	10 (1-54)
Time to undetectable HBV DNA (months), median (range)	3 (1-5)	3 (1-15)
Additional treatment after HBeAg seroconversion or loss (months), median (range)	16 (6-49)	25 (6-60)
Median total	24 (12-54)	36 (18-89)

*When HBV DNA increased to >104 copies/mL, an extra visit a week apart was required for confirmation, viral relapse was confirmed by increased serial HBV DNA levels in two consecutive samples at least 1 weeks apart.

			treatment duration (months) (range)						
			*Group A, HBeAg seroconversion group; group B, HBeAg loss group						

Results:

Table 1. Cumulative relapse rate after lamivudine cessation

Follow up (months)	Group A (HBeAg seroconversion), n (%)	Group B (HBeAg loss), n (%)
1	0 (0)	0 (0)
2	9 (11)	8 (18.6)
3	12 (14.6)	10 (23.3)
4	13 (15.9)	12 (27.9)
6	17 (20.8)	12 (27.9)
9	18 (22.1)	14 (32.6)
12	19 (23.4)	15 (35)
18	20 (25)	16 (37.7)
24	20 (25)	16 (37.7)
36*	20 (25)	17 (41.1)
48	21 (29.4)	17 (41.1)
60	21 (29.4)	17 (41.1)

*47/82 (57.3%) in group A and 31/43 (70%) in group B were followed up for at least 3 years.

All relapsers had the reappearance of serum HBV DNA, but HBeAg reappearances were found in only 9/21 (42.9%) relapsers in group A and 13/17 (76.5%) in group B.

Cumulative relapse rate stratified by total treatment duration in group A (total N = 82) (HBeAg seroconversion group).

	5-year cumulative relapse rate*
<18 months total treatment	43/72 (60%)
≥ 18 months total treatment	3/10 (25.1%)

*log rank test p=0.002

Author's conclusion: For patients who maintained HBeAg seroconversion for ≥6 months and total duration for ≥18 months, lamivudine withdrawal is a reasonable option. Prolonged treatment may be required for patients aged greater than 30 years to reduce relapse.
Additional results: relapse rate by age (< vs. ≥30y)

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Gramenzi 2011	Retrospective cohort study	N= 42 HBeAg negative and NA naïve	Recruitment/setting: participants were consecutively enrolled in a single centre open-label study on long term lamivudine monotherapy (150mg/day) from Sept 1996 to Feb 2005. Inclusion: HBeAg negative patients. Age above 18y; CHB infection (HBsAg positivity ≥ months); HBeAg negativity/anti-HBe positivity in at least two determinations in the last 6 months before therapy; detectable serum HBV DNA within the last month before therapy. Exclusion: Previous treatment with NA; immunosuppressive treatment in the last 6 months; infection with HDV, HCV and/or HIV; liver cirrhosis of Child Pugh class B or C, HCC, liver transplantation and causes of liver disease other than HBV. Baseline characteristics Number: 42 Mean age, years (SD): 49 ± 11 Male/female (%): 33/9 (79/21) HBV DNA, log10 IU/mL, mean ±SD: 5.97 ±1.34 ALT (U/L), mean ±SD: 197±136	Serum HBsAg levels, measured every 6 months by Architect assay (Abbott Diagnostics), calibrated against the WHO standard, allowing the quantification of HBsAg from 0.05 to 250IU/mL HBV DNA, measured by real-time PCR (Roche diagnostics; lower limit of detection 6IU/mL) before and every 3 months.	N/A	1.virological breakthrough, defined by an increase in viral load >1 log10 IU/mL when compared to the nadir achieved under antiviral treatment in at least two consecutive determinations (also defined as treatment failures).	Not stated.

Previous IFN treatment (%) Chronic active hepatitis Cirrhosis	19 945) 15 (79) 4 (21)
HBV genotype (%) A B C D	 2 (5) 0 2(5) 38(90)
Log10 HBsAg (IU/mL), mean ±SD	3.39 ±0.47
Cirrhosis, n (%)	9 (21)

Results:

Table 1. Cumulative incidence of viral breakthrough (median time of 27 months, 95% CI=22-32 months)

12 months	3 (7%)
24 months	11 (27%)
36 months	26 (63%)
60 months	31 (73%)

To identify the HBsAg drop able to predict virologic breakthrough, changes between pretreatment and month 6 levels were analysed. The ROC curve showed a change in HBsAg level ≥0.7 log10 IU/mL was the best trade-off between sensitivity (100%) and specificity (50%).

Table 2. The proportion of patients with decrease of < or ≥ 0.7 log10 IU/mL in HBsAg at month 6 of lamivudine treatment on virological breakthrough (N=41)

	<0.7 log10 IU/mL	≥0.7 log10 IU/mL
Virologic breakthrough	35/38 (92%)*	0/3 (0%)
No virologic breakthrough	3/38 (8%)	3/3 (100%)**

*Positive predictive value (PPV) = 92%

**Negative predictive value (NPV) = 100%

PPV is the proportion of people with the outcome who are correctly diagnosed.

Table 3. The proportion of patients with undetectable/detectable HBV DNA at month 6 of lamivudine treatment on virological breakthrough (N=41)

	Undetectable HBV DNA	Detectable HBV DNA
Virologic breakthrough	12/13 (93%)*	23/28 (82%)
No virologic breakthrough	1/13 (7%)	5/28 (18%)**

*Positive predictive value (PPV) = 93%

**Negative predictive value (NPV) = 18%

Table 4.The proportion of HBV DNA negative patients with decrease of < or ≥ 0.7 log10 IU/mL in HBsAg at month 6 of lamivudine treatment on virological breakthrough (N=28)

	<0.7 log10 IU/mL	≥0.7 log10 IU/mL
Virologic breakthrough	23/25 (92%)*	0/3 (0%)
No virologic breakthrough	2/25 (8%)	3/3 (100%)**

*PPV = 92%

**NPV = 100%

Author's conclusion: The results of this study with a small sample size suggest a role of on-treatment HBsAg quantification in the management of lamivudine-treated patients. If validated prospectively in a larger patient cohort, HBsAg measurements would be a useful adjunct to optimise antiviral therapy.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Yoon 2005	Prospective cohort	N= 461 M: 335 F: 126	Recruitment/setting: enrolled at the Kangnam St Mary's Hospital Korea between 1998 and 2003; aged 27-71 (mean 38.7) years; HBsAg, HBeAg, HBV DNA positive for at least 6 months before LAM. Inclusion: HBeAg positive CHB, elevated serum ALT level (concentrations >1.5 x ULN) for at least 6 months before therapy. No patient had evidence of hepatic decompensation such as ascites, variceal bleeding or hepatic encephalopathy. On LAM	HBeAg seroconversion, measured by radio-immunoassay HBeAg loss, measured by radio-		1. Virologic breakthrough (the reappearance of HBV DNA after an initial response during treatment)	Grant of the Korean Health 21 Research and Development Project from the Ministry of Health and

			treatment (100mg/d) for more than 12 months Exclusion: see above. Baseline characteristics N (%) Age, years: 38.7 ± 13.0 Sex Male:female: 335: 126 ALT, IU/L (median, range): 135 (51-2055) Total bilirubin, mg/dl: 1.5 ± 0.9 HBV DNA qualification by PCR (n=198): All positive (100%) HBV DNA quantitative by b-DNA (median, range), p/ml (n=263): 969 (4.2-20907) HBV genotype: C (100%) Duration of LAM treatment, months: 25.8 ± 13.9	immunoassay HBsAg loss Resistance measured by virologic breakthrough Patients were followed up either monthly or bimonthly HBV DNA measured by PCR (detection limit 2.5pg/mL) Patients who stopped LAM were followed up at 1 or 2 month intervals for a mean period of 40.7 (range 12-75) months			Welfare, South Korea

Results:

During LAM therapy

	Cumulative n (cumulative %)
HBeAg seroconversion at:	
Year 1 (N=461)	106 (22.9)
Year 2 (N=177)	153 (33.2)
Year 3 (N=65)	219 (47.6)
Year 4 (N=25)	250 (54.2)
Year 5 (N=6)	271 (58.8)

HBeAg loss at:	
Year 1	(28.9)
Year 2	(44.2)
Year 3	(58.6)
Year 4	(67.7)
Year 5	(70.9)
Virological breakthrough* at:	
Year 1 (N=461)	38 (8.2)
Year 2 (N=173)	192 (41.7)
Year 3 (N=66)	257 (55.7)
Year 4 (N=22)	299 (64.8)
HBsAg loss	0

*virologic breakthrough was considered as the reappearance of HBV DNA after initial response during treatment.

Additional results: patients with HBeAg seroconversion also showed higher levels of pre-treatment serum ALT than those without.

At the time of stopping treatment (patients who discontinued treatment early) (n=114):

	N (%)
HBeAg seroconversion	95 (20.6)
HBeAg loss	19 (4.1

Additional results: post treatment cumulative relapse rates in HBeAg loss alone and HBeAg seroconversion groups. Results on composite outcomes.

Mean time to achieve HBeAg seroconversion: 13.3 (1-55) months

Patients who were treated for less than 12 months after HBeAg seroconversion relapsed more frequently (p=0.003).

Author's conclusion: Results suggest that additional treatment for over 12 months after HBeAg seroconversion in younger patients may produce a better long-term outcome.

Reference	Study type/ Study	Number of	Patient characteristics	Prognostic factor(s)	Length of	Outcome measures	Source of funding

	quality	patients			follow-up		
Park 2005	Retrospective study	N= 340	Recruitment/setting: South Korea Inclusion: HBeAg positive naïve CHB patients treated with lamivudine (100mg once daily) (mean duration: 18.7 (range 6-56) months). All patients had >ULN x 2 ALT, as well as HBsAg, HBeAg, and HBV DNA for at least 6 months before start of lamivudine therapy; had no history of previous IFN therapy. None had clinical cirrhosis Exclusion: HCV, HDV and HIV and autoimmune hepatitis Baseline characteristics Mean age years ± SD (range): 38.2 ± 10.1 (17-66) M:F: 285:55 ALT (IU/L): 280 ± 243 (80-1780) ≥2- <5 x ULN: 181 (53.2%) ≥5 x ULN: 159 (46.8%) HBV DNA (pg/mL), mean ±SD, log 10: ± 1.18 (0.08-3.78) HBeAg level, mean ±SD: 228 ± 165 (1.1-806)	Serum HBeAg Anti-HBe HBV DNA ALT Measured every 1 or 2 months until HBeAg seroconversion (serial monitoring) HBV measured with hybridisation capture assay (lower limit of detection 0.5pg/mL) Serum HBeAg and anti-HBe levels were measured by microparticle enzyme immunoassy	N/A	Viral breakthrough – reappearance of HBV DNA in serum on two or more occasions after its initial disappearance Viral response A simultaneous HBeAg seroconversion and HBV DNA negativity on two occasions at least 1 month apart	Not stated
Results: HBeAg seroconversion was achieved in 109 (32.1%) patients. Mean time to HBeAg seroconversion was 9.4 ± 8.0 (range 1-52) months Cumulative rates of seroconversion at 6,12,24,36 months were 14, 22, 31, 40%. Viral breakthrough was observed in 82 (24.1%) patients at a mean of 16.8 ± 6.8 (range 7-40) months after start of lamivudine therapy.							

Cumulative breakthrough rates at 12, 18, 24 and 36 months were 9, 26, 42 and 59%

Biochemical breakthrough was observed in 80 at a mean of 3.9 (range 0-10) months after onset of viral breakthrough, while 2 patients had no serum ALT elevation 6-28 months.

Table 1. Mean HBeAg levels (sample rate/cut off rate) at monthly intervals during lamivudine therapy according to the types of response (responders, nonresponders, breakthrough)*

Week	0	4	8	12	16	24	32	40	48
Responders	170.2	73.3	18.8	17.2	16.9	9.7	9	4.7	4.3
Non-responders	252.5	158.8	124	138.9	116.8	108.6	85.6	100.9	102.7
Breakthroughs	264.6	198.2	165.5	119.2	112.2	82.8	71.6	79.3	92.3

*mean HBeAg levels were significantly lower in the responders than in nonresponder and breakthrough groups (p<0.001)

Table 2. Distribution of the maximal decrease of HBeAg level since the start of lamivudine therapy by types of response

	Maximal decrease of HBeAg				
	<50%	50-74%	75-89%	90-98%	>99%
Responders (n=109)	1	3	2	31	72
Nonresponders (n=149)	37	36	29	38	9
Breakthroughs (n=82)	13	29	13	20	7

103/109 showed a decrease of >90% of the pre-treatment HBeAg values for the maximal reduction rate during lamivudine therapy.

Three groups were created according to reduction rates (compared with pre-treatment HBeAg levels, by serial monitoring during LAM therapy):

Continuously decreasing HBeAg levels of >90% pf pretreatment values over time (n=195)

A continuous decrease to >90% of pre-treatment values, and then progressively increasing of HBeAg levels(n=65)

No change or fluctuation group (n=80)

Table 3.

	Continuous decrease of >90% of pre-treatment HBeAg values (n=195)	No change/fluctuation (n=80)	Continuous decrease of >90% of pre-treatment HBeAg values, then progressively increasing HBeAg levels (n=65)

Responders (n=109)	53.8%	2.5%	3.1%
Non-responders (n=149)	42.1%	71.2 %	15.4%
Breakthroughs (n=82)	4.1%	26.3%	81.5%

Table 4. Odds ratios of predictive factors of HBeAg seroconversion and viral breakthrough using multivariate* stepwise Cox's regression model

	OR HBeAg seroconversion (95% CI)
Continuously decreasing HBeAg levels of >90% of pretreatment values over time	14.64 (3.49-61.5)*
	OR Viral breakthrough (95% CI)
Continuous decrease of >90% of pre-treatment HBeAg values, then progressively increasing HBeAg levels	19.7 (7.74-49.97)**
No change or fluctuation	10.17 (3.83-27.0)**

*compared to referent group of patients who had a continuous decrease of >90% of pre-treatment HBeAg values, then progressively increasing HBeAg levels and no change or fluctuation group (OR=1.00).

**compared to referent group of patient who had a continuously decreasing HBeAg levels of >90% of pretreatment values over time (OR=1.00).

Author's conclusion: Pre-treatment quantitative HBeAg levels during lamivudine therapy in addition to other clinical parameters allow the selection of patients who will benegit from lamivudine therapy. The changing patterns of quantitative HBeAg levels by serial monitoring during lamivudine therapy may allow not only the prediction of treatment responses, but also an early recognition of a viral breakthrough.

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Thompson	Prospective follow up	N=85	A mixed group of HBeAg negative and positive patients with presence of HBsAg in serum for more	HBV DNA (measured by	Median follow up	1) HBeAg seroconversion	None

<table>
<tr>
<td>2007</td>
<td>study in Melbourne</td>
<td></td>
<td>than 6 months and elevated ALT and detectable HBV DNA by the hybridization assay prior receiving lamivudine therapy. All patients who had completed at least 6 months of lamivudine treatment (100mg daily orally) were included in this follow up study. When patients developed LAM resistance, they were treated with adefovir add on at diagnosis.
Baseline characteristics
<table>
<tr><th></th><th>HBeAg positive (n=47)</th><th>HBeAg negative (n=38)</th><th>P value</th></tr>
<tr><td>Age (years)</td><td>37 (33.7-40.3)</td><td>44.5 (41.5-47.5)</td><td>0.002</td></tr>
<tr><td>Sex, n (%) male</td><td>32 (68%)</td><td>35 (92%)</td><td>0.008</td></tr>
<tr><td>Serum ALT (IU/L)</td><td>176 (103.2-248.8)</td><td>155.8 (113.6-198)</td><td>0.7</td></tr>
<tr><td>HBV DNA (pg/ml)</td><td>947 (569.2-1324.8)</td><td>336 (141.4-530.6)</td><td>0.01</td></tr>
<tr><td>A1762t/G1764A variant</td><td>19/33</td><td>21/32</td><td>0.18</td></tr>
<tr><td>G1896A variant</td><td>3/33</td><td>18/32</td><td><0.001</td></tr>
<tr><td>Biopsy (n)
-Mid/moderate (F1/2)
-Advanced (F3/4)
-Cirrhotic (F4)</td><td>

33
19
3</td><td>

21
12
5</td><td>

0.49
0.49
0.45</td></tr>
</table>
</td>
<td>the Dignere Hybrid Capture II assay with lower detection limit of this test 0.5 pg/ml (or 105 copies/ml).
HBV DNA was measured every 3 months in the follow up period.</td>
<td>was 19 months, (range 6-54 months)</td>
<td>(defined as the loss of HbeAg and the appearance of anti-Hbe)

2) Lamivudine resistance (patients who were suspected of LAM resistance due to increase in viral load, or reappearance of HBV DNA in a patient with previously undetectable HBV DNA were tested by sequencing on the polymerase gene). Pretreatment serum was then tested retrospectively in these patients to exclude pre existing LAM resistant mutations</td>
<td>mentioned.</td>
</tr>
</table>

Results:

The rate of seroconversion increased over time, to reach 35% by 24 months and 75% by 36 months, although only 8 HbeAg positive patients reached this time point. The authors reported that there were no predictor factors of HbeAg seroconversion, analysis being limited by sample size

The authors reported that no patient developed lamivudine resistance prior to 9 months of therapy; the proportion of patients who developed lamivudine resistance was 6%, 31% and 51% at 12, 24 and 48 months.

Table. 1 Predictors of early development of lamivudine resistance

	Outcome: development of LAM resistance (n=26)		
Prognostic factors	Baseline	Risk Ratio (95% C.I)*	P-value*
Detectable DNA (>105 copies/ml) at 6 months of lamivudine treatment	No	4.73 (1.49, 15.0)	0.008

*Risk Ratio is given for the development of LAM resistance from a Cox proporotional hazards model including the following variables: age, gender, ethnic background, baseline HBV DNA and ALT levels, HbeAg status, fibrosis score, advanced fibrosis (F3/4), genotype, precore mutation at baseline in a sample of 54 patients (the defined censor events for this analysis were development of LAM resistance (n=26), treatment cessation (n=27), continued therapy (n=29) or loss to follow up (n=3).

(Risk ratio is the ratio of incidence rate in patients with LAM resistance divided by incidence rate in patients with no LAM resistance)

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Hsieh 2009	Retrospective study Mean treatment duration: 21.3 months (range 6-54)	N= 40	Recruitment/setting: gastroenterology clinics of the National Taiwan University Hospital (July 1997-Aug 2002). All were positive for HBsAg for at least 6 months before enrolment and negative for antibody against HCV, HDV and HIV. Inclusion: CHB patients who developed resistance after LAM therapy Exclusion: Baseline characteristics	ALT levels HBeAg monitored at least every 3 months HBV genotype was done by direct sequencing when a biochemical breakthrough occurred	N/A Statistical method: multivariate logistic regression and linear regression	1. Lamivudine resistance (detectable mutation strain within 12 months of treatment)	Grant from the National Taiwan University Hospital; DoH and the National Science Council; Executive

			<table><tr><td></td><td>Genotype B (n=24)</td><td>Genotype C (n=16)</td></tr><tr><td>Mean age, years (SD)</td><td>39.2 ± 2.6</td><td>35.0 ± 3.3</td></tr><tr><td>Male/female (%)</td><td>21 (87.55)/ 3 (12.5%)</td><td>14 (87.5%)/ 2 (12.5%)</td></tr><tr><td>HBV DNA, log10 IU/mL, mean ±SD</td><td>8.04 ±7.56</td><td>7.86±7.48</td></tr><tr><td>ALT (U/L), mean ±SD</td><td>399.3 ± 74.5</td><td>288.5 ± 99.5</td></tr><tr><td>HBeAg positive/ negative, n (%)</td><td>14 (58.3%)/ 10 (41.7%)</td><td>12 (75%)/ 4 (25%)</td></tr><tr><td>Time to first resistant strain, month (range)</td><td>17.2 ± 2.2 (7-47)</td><td>23.3 ± 2.4 (10-48)</td></tr><tr><td>Early emergence of LAM-R strain* (positive/negative), n</td><td>13/11</td><td>2/14</td></tr></table> *defined as detectable mutation strain within 12 months of treatment.	HBV DNA levels measured only when clinically indicated, using real time PCR assay (detection limit of 100 copies/mL)			Yuan; national Health Research Institutes; Liver Disease Prevention and Treatment Research Foundation

Results:

Mean interval between start of lamivudine therapy and detection of lamivudine-R strains was 19.6 months (range 7-48).

Genotype B patients tended to have a shorter interval to develop lamivudine resistance than genotype C patients (17.2 vs. 23.3 months; p=0.06).

In terms of early emergence of lamivudine resistance, genotype B is significantly associated with development of lamivudine resistance within the first 12 months (p=0.004) compared with genotype C (odds ratio = 8.27; p=0.004).

Cumulative incidence of lamivudine resistance over time by HBV genotypes

	Cumulative incidence of LAM resistance over time	
Months	Genotype B (n=24)	Genotype C (n=16)

0	0%	0%
6	0%	0%
12	10 (43%)	1 (8%)
18	15 (61%)	5 (34%)
24	19 (80%)	7 (46%)
28	21 (87%)	13 (80%)
36	21 (87%)	15 (91%)
42	23 (94%)	15 (91%)
48	24 (100%)	16 (100%)

Author's conclusion: Mutation patterns of YMDD motif do not different between Taiwanese HBV genotype B and C patients. Compared with HBV genotype C, genotype B appears to have an earlier biochemical resistance to lamivudine than genotype C. More frequent monitoring of viral load or genotypical resistance might be needed for patients with HBV genotype B infection receiving lamivudine therapy, especially during the first year.

E.7.6 Patients with CHB on adefovir treatment

Reference	Study type	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding	
Llop 2009	Retrospective study Small sample size Two groups of	N= 66 On LAM (n=31) or ADV (n=35) treatment	Recruitment/setting: Clinical records reviewed retrospectively. University hospital, Spain Inclusion: CHB patients treated with LAM or ADV between 2001 and 2006. Exclusion: people with cirrhosis or hepatocellular carcinoma on antiviral therapy. Baseline characteristics	Viral DNA measured at month 1, 3 and 6	N/A	Virologic response – defined as undetectable HBV DNA (<200 copies)	Not stated.	

	treatment were analysed independently.					Biochemical response – defined as normalisation of ALT (ULN 40 IU/L)		

	LAM (n=31)	ADV (n=35)
Age at treatment onset (years), mean (SD)	38 (12)	42 (14)
Sex, n Male:female	 24:7	 31:4
Transmission,n Transfusion Sexual Perinatal Surgery Surgery	 6 1 3 1 20	 4 4 2 1 24
HBeAg, n Positive Negative	 10 21	 11 24
Previous treatment,n IFN or peg IFN LAM	 10 0	 2 24

Results

Table 1. Differences in pattern of viral load decrease in responders vs. nonresponders (virologic response at 1 year) to LAM and ADV

Prognostic factors	Weeks	LAM		ADV	
		Responders	Non responders	Responders	Non responders
Mean viral load decrease (in log)	4 12 24	1.2 (±1.8) 2.7 (±0.99) 2.8 (±1.2)	2.7 (±1.3) 2.7 (±1.5) 3.5 (±1.3)	1.6 (±1.1) 2.4 (±1.1) 2.6 (±1.2)	0.8 (±1.4) 1.3 (±1.3) 1.3 (±1.2)
Mean viral load decrease from baseline (%)	4 12 24	19.5 (±26.3) 49.2 (±13.2) 52.1 (±14.5)	33.5 (±13.6) 38.3 (±20.4) 50.8 (±15.4)	32.1 (±17.6) 46.6 (±13.9) 49.3 (±12.7)	11 (±21.9) 19.9 (±20) 21.1 (±19.8)

Table 2.ROC curves (AUC) at week 12 from treatment onset with lamivudine

	AUC
Viral load decrease from baseline (%)	0.675

A % of viral load decrease from baseline ≤30% had a sensitivity of 92% and a negative predictive value of 80%.

Table 3. ROC curves (AUC) at week 12 and 24 from treatment onset with adefovir

Adefovir	AUC
Viral load decrease from baseline (%)	
Week 12	0.83
Week 24	0.9
Decrease in log viral load	
Week 12	0.77
Week 24	0.79

At week 24 a decrease in viral load of 1 log had 93% sensitivity and 80% negative predictive value

A % of viral load decrease from baseline ≤20% had 100% sensitivity and 100% negative predictive value.

AUC = Area under the ROC curve, or c statistics, ranges from 0.5 (no discrimination) to a theoretical maximum of 1 (perfect discrimination).

ROC curve = A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 – specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.

Author's conclusion: The decrease in viral DNA at weeks 12 and 24 can predict virologic response at 1 year in patients with CHB treated with LAM or ADV.

E.7.7 Patients with CHB on entecavir treatment

Bibliographic	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-	Outcome measures	Source of funding

<table>
<tr><th>reference</th><th></th><th></th><th></th><th></th><th>up</th><th></th><th></th></tr>
<tr><td>Lee 2011A</td><td>Prospective cohort study in South Korea</td><td>N=101 (59 HbeAg positive and 42 HbeAg negative patients)</td><td>HbeAg positive and negative patients with CHB (positive for HbsAg for at least 6 months) during entecavir treatment (0.5mg/daily) for >12 months and 58 patients continuied >24 months (previously treatment naïve patients). Exclusion criteria: patients with hepatocellular carcinoma, or other concomitant diseases, hepatitis C, autoimmune disease, alcoholic liver disease.
<table>
<tr><td colspan="3">Baseline characteristics</td></tr>
<tr><td></td><td>HbeAg (+)</td><td>HbeAg (-)</td></tr>
<tr><td>Mean age, yrs (SD)</td><td>41.3 (9.57)</td><td>46.6 (8.49)</td></tr>
<tr><td>Male, n(%)</td><td>44 (74.6%)</td><td>30 (71.4%)</td></tr>
<tr><td>Mean HbsAg, log10 IU/ml)</td><td>3.51 (1.06)</td><td>3.06 (0.69)</td></tr>
<tr><td>Mean ALT</td><td>227.5 (274.31)</td><td>163.21 (121.89)</td></tr>
<tr><td>Mean AST</td><td>150.5 (201.15)</td><td>111.07 (84.25)</td></tr>
<tr><td>Mean GGT</td><td>72.58 (45.33)</td><td>62.07 (33.01)</td></tr>
<tr><td>HBV DNA, log copies/ml >8</td><td>38 (64.4%)</td><td>38 (64.4%)</td></tr>
</table></td><td>1) HBV DNA:using b-DNA assay until Dec 2008 (lower limit of detection: 2000 copies/ml)
-after Dec 2008 using PCR assay (lower limit of detection: 50 copies/ml) (*samples at 6,12 months were retested suing PCR assay)
2) HbsAg was quantified using the Architest HbsAg assay (dynamic range 0.05-250.0 IU/ml)</td><td>12 and 24 months</td><td>Treatment response:
For HbeAg (+): defined as serum HBV DNA undetectable or HbeAg loss/seroconversion.
For HbeAg (-): defined as serum HBV DNA undetectable.</td><td>Biobank of Ajou University Hospital (a Biobank in the KORBIN network)</td></tr>
</table>

			<=8	21 (35.6%)	30 (71.4%)			
			Liver cirrhosis, n (%)	11 (18.6%)	20 (47.6%)			
			Viral breakthrough	0	0			
			Undetectable HBV DNA, n(%) -12 m -24 m	 24 (40.7%) 25 (71.4%)	 28 (66.7%) 21 (92.3%)			
			ALT normalization, n(%) -12 m -24 m	 47 (79.7%) 28 (80%)	 30 (71.4%) 14 (60.9%)			
			HbeAg loss, n(%) -12 m -24 m	 11 (18.6%) 11 (31.4%)				
			HbeAg seroconversion, n(%) -12 m -24 m	 9 (15.3%) 7 (20%)				
Results: For HbeAg positive patients								

Prognostic factors	Outcome: Undetectable HBV DNA (by PCR) at 12 months		P value/ Results of the multivariate analysis**	Outcome: Undetectable HBV DNA (by PCR) at 24 months		Results of the multivariate analysis**
	% of patients with undetectable HBV DNA (n=24)	% of patients with detectable HBV DNA (n=35)		% of patients with undetectable HBV DNA (n=25)	% of patients with detectable HBV DNA (n=10)	
Undetectable HBV DNA by PCR, n (%) -3 months(<2000 copies/ml) -6 months -12 months	 12 (52.2%) 12 (50%)	 2 (6.3%) 4 (11.4%)	 0.001 0.092	 9 (39.1%) 10 (40%) 16 (64%)	 0 0 0	 0.686 0.408 0.998
Mean HbsAg, log 10 IU/ml, mean (SD) - Baseline -3 months -6 months -12 months	 3.26 (1.11) 2.83 (1.07) 3.06 (0.97)	 3. 86 (1.01) 3.49 (0.89) 3.52 (0.78)	 0.423	 3.23 (1.11) 2.82 (1.09) 2.97 (1.00) 3.04 (0.82)	 4. 33 (0.76) 4.01 (0.40) 3.98 (0.38) 3.87 (0.25)	 0.218 0.982 0.253 0.219
HbsAg <3000 IU/ml at 3 months, n (%)	17 (77.3%)	14 (43.8%)	0.173	17 (77.3%)	14 (43.8%)	0.010

*Results were adjusted for age, gender, mean albumin, mean platelet (103/mm2), mean AST, mean ALT, mean TB, liver cirrhosis, HBV DNA baseline, mean HbsAg (log10 IU/ml), HbsAg<3000 IU/ml at 3 months

Prognostic factors	Outcome: HbeAg loss/seroconversion at 12 months		P value/ Results of the multivariate analysis*	Outcome: HbeAg loss/seroconversion at 24 months		Results of the multivariate analysis*
	% of patients with HbeAg loss/seroconverted (n=20)	% of patients with no experience of HbeAg loss/seroconversion (n=39)		% of patients with HbeAg loss/seroconverted (n=18)	% of patients with no experience of HbeAg loss/seroconversion (n=17)	

Undetectable HBV DNA by PCR, n (%) -3 months -6 months -12 months	 9 (47.4%) 9 (45%)	 5 (13.9%) 7 (17.9%)	 0.046 0.884	 7 (43.8%) 7 (38.9%) 11 (61.1%)	 2 (12.5%) 3 (17.6%) 5 (29.4%)	 NS in univariate analysis
Mean HbsAg, log 10 IU/ml, mean (SD) - Baseline -3 months -6 months -12 months	 2.98 (1.26) 2.72 (1.21) 2.85 (1.10)	 3. 79 (0.83) 3.49 (0.79) 3.60 (0.60)	 0.629 0.601 0.550	 2.98 (1.19) 2.71 (1.27) 2.85 (1.12) 2.98 (0.93)	 4.14 (0.67) 3.60 (0.65) 3.73 (0.47) 3.59 (0.49)	 0.046 0.239 0.239 0.438
HbsAg <3000 IU/ml at 3 months, n (%)	16 (84.2%)	15 (42.9%)	0.026	12 (75%)	6 (37.5%)	NS in univariate analysis

**Results were adjusted for mean Hb, mg/dl (SD), mean HbsAg (log10 IU/ml), HbsAg<3000 IU/ml at 3 months

……

For HbeAg negative patients:

Prognostic factors	Outcome: Undetectable HBV DNA (by PCR) at 12 months		P value/ Results of the multivariate analysis***
	% of patients with undetectable HBV DNA (n=28)	% of patients with detectable HBV DNA (n=14)	
Undetectable HBV DNA by PCR, n (%) -3 months -6 months	 22 (78.6%) 18 (64.3%)	 8 (57.1%) 2 (14.3%)	 NS in univariate analysis 0.008
Mean HbsAg, log 10 IU/ml, mean (SD) - Baseline -3 months -6 months	 2.98 (0.79) 3.05 (0.53) 3.18 (0.56)	 3. 22 (0.42) 3.16 (0.35) 3.24 (0.34)	 NS in univariate analysis NS in univariate analysis NS in univariate analysis

HbsAg <3000 IU/ml at 3 months, n (%)	19 (70.4%)	11 (78.6%)	NS in univariate analysis

*** Results were adjusted for liver cirrhosis, undetectable HBV DNA, mean HbsAg, HbsAg <3000 IU/ml at 3 months

NS: non statistically significant

Conclusions:

For HbeAg positive patients:

undetectable HBV DNA (<2000 copies/ml) at 3 months was an independent predictor of undetecteble HBV DNA at 12 months after adjusting for the effect of age, gender, mean albumin, mean platelet (103/mm2), mean AST, mean ALT, mean TB, liver cirrhosis, HBV DNA baseline, mean HbsAg (log10 IU/ml), HbsAg<3000 IU/ml at 3 months

HbsAg <3000 IU/ml at 3 months was an independent predictor of undetecteble HBV DNA at 24 months after adjusting for the effect of age, gender, mean albumin, mean platelet (103/mm2), mean AST, mean ALT, mean TB, liver cirrhosis, HBV DNA baseline, mean HbsAg (log10 IU/ml), HbsAg<3000 IU/ml at 3 months

undetectable HBV DNA (<2000 copies/ml) at 3 months was an independent predictor of HbeAg loss/seroconversion at 12 months after adjusting for the effect of mean Hb, mg/dl (SD), mean HbsAg (log10 IU/ml), HbsAg<3000 IU/ml at 3 months

HbsAg (log IU/ml) at baseline was an independent predictor of HbeAg loss/seroconversion at 24 months after adjusting for the effect of mean Hb, mg/dl (SD), mean HbsAg (log10 IU/ml), HbsAg<3000 IU/ml at 3 months

For HbeAg negative patients:

undetectable HBV DNA at 6 months was an independent predictor of undetecteble HBV DNA at 12 months after adjusting for the effect of liver cirrhosis, undetectable HBV DNA, mean HbsAg, HbsAg <3000 IU/ml at 3 months

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Jung 2010A	Prospective hospital based study at Korea	N=51, Response rate 28/51 (54.9%) (reasons for	HbeAg positive treatment naïve CHB patients receiving entecavir (0.5mg/daily) for more than 1 year (median duration was 21 months (range 18-24 months) Baseline characteristics HbsAg response | HbsAg no response | Total (N=28)	1) ALT normalization 2) undetectable HBV DNA (measured by Cobas Taqman; lower detection	3,6 and 12 months after entecavir treatment	HbsAg response: decrease in the HbsAg level>1log10 IU/ml from baseline at 12 months after	Supported by Korean University Grant (K0823371)

		patients not participated in the study unclear)					limit 1.84 log10 IU/ml) 3) HbeAg loss 4) HbeAg seroconversion		entecavir treatment -HbsAg levels were measured using the Architect HbsAg QT assay at baseline, 6 and 12 months after entecavir treatment	

	(N=5)	(N=23)	
Age (y), mean (SD)	36.6 (11)	37 (10.6)	37 (10)
Sex (male)	4 (80)	20 (87)	24 (86)
Total bilirubin (mg/dL	0.93 (0.39)	1.25 (1.74)	1.2 (1.6)
Albumin	4.1 (0.37)	4.32 (0.44)	4.3 (0.4)
ALT (IU/ml)	277 (157)	188 (130)	204 (136)
HBV DNA (log10 copies/ml)	8.16 (0.36)	8.03 (0.63)	8.1 (0.6)
HbsAg concentration (log10 copies/ml)	4.40 (0.48)	4.0 (0.49)	4.0 (0.5)

Results:

At 12 months after entecavir treatment, 5 patients (17.8%) showed HbsAg response (decrease >1log10 IU/ml from baseline level)

Cumulative incidence of prognostic factors between those patients with a HbsAg response and those without at the end of 1 year after entecavir treatment

Cumulative incidence* of prognostic factors	HbsAg response (N=5)	HbsAg no response (N=23)	P value
ALT normalization	5/5 (100%)	19/23 (83%)	NS
Undetectable HBV DNA (<1.84 log10 IU/ml)	5/5 (100%)	16/23 (70%)	NS

HbeAg loss	4/5 (80%)	7/23 (30%)	0.034
HbeAg seroconversion	2/5 (40%)	7/23 (30%)	NS

*Cumulative incidence is defined as the probability that a particular event, such as occurrence of a particular disease, has occurred before a given time

In conclusion: only the cumulative incidence of HbeAg loss after 1 year of entecavir treatment was significantly higher in patients with HbsAg response than in patients without response .

<table>
<tr><th>Bibliographic reference</th><th>Study type/ Study quality</th><th>Number of patients</th><th>Patient characteristics</th><th>Prognostic factor(s)</th><th>Length of follow-up</th><th>Outcome measures</th><th>Source of funding</th></tr>
<tr><td>Chon 2011</td><td>Prospective cohort study in Korea
-Between March 2007 and December 2009, treatment naïve patients witch CHB starting antiviral therapy with entecavir 0.5 mg/daily were prospectively enrolled.</td><td>N=420 (245 were lost; 22 were lost to follow up, 20 showed poor compliance, 8 were primary non responders, 195 were followed up for less than 2 years).</td><td>Patients older than 16 years old with persistent serum HbsAg for >6 months and HBV genotype C. Exclusion criteria: decompensated liver cirrhosis, previous antiviral treatment for CHB (either interferon or NUC), current use of corticosteroid or immunomodulatory drugs, co-infection with hepatitis C, D or HIV, serious concurrent medical illness, evidence of HCC or prior organ transplantation.
Baseline characteristics
<table>
<tr><th></th><th>All patients</th><th>Patients with VR</th><th>Patients without VR</th></tr>
<tr><td>Patient numbers</td><td>175 (100%)</td><td>139 (79.4%)</td><td>36 (20.6%)</td></tr>
<tr><td>Mean age, yrs (SD)</td><td>45 (11)</td><td>46 (11)</td><td>42 (11)</td></tr>
<tr><td>HbeAg (+)</td><td>126 (72%)</td><td>100 (71.9%)</td><td>26 (72.2%)</td></tr>
<tr><td>cirrhosis</td><td>61 (34.9%)</td><td>52 (37.4%)</td><td>9 (25%)</td></tr>
<tr><td>Mean ALT (IU/L)</td><td>61 (34.9)</td><td>181 (288)</td><td>107 (75)</td></tr>
</table></td><td>1) HBV DNA levels
2) HBV DNA reduction from baseline</td><td>Up to 2 years (24, 48 and 92 weeks)</td><td>Virological response: undetectable HBV DNA by PCR (<12 IU/ml)</td><td>A grant of the Bilateral International Collaborative R&D Programme from the Ministry of Knowledge Economy and by the Good Health R&D Project from the Ministry for Health, Welfare and Family Affairs, Republic of Korea (A050021).</td></tr>
</table>

			Mean HBV DNA (log10 copies/ml)	7.03 (1.31)	6.84 (1.24)	7.74 (1.36)			

Results:

After 2 years of entecavir treatment, 139 patients (79.4%) achieved VR; 89 (73.6%) were HbeAg positive and 50 (92.6%) HbeAg negative.

Prognostic factors	Outcome: virological response at 96 weeks AUC (area under the curve)*	P value	
HBV DNA level at 24 weeks	0.824	P= 0.023	
HBV DNA level at 48 weeks	0.908		
HBV DNA reduction at 24 weeks	0.667	P= 0.256	
HBV DNA reduction at 48 weeks	0.719		

* AUC is the area under the curve in a graphical presentation of sensitivity of a discriminant factor against 1- specificity to predict an outcome. The predictive power of a discriminant factor depends on how well this factor separates the group being tested into those with and without the outcome tested. An AUC of 1 represents a perfect discriminant factor; an AUC of .5 represents a worthless test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system:

.90-1 = excellent (A)

.80-.90 = good (B)

.70-.80 = fair (C)

.60-.70 = poor (D)

.50-.60 = fail (F)

Based on the previous results, the authors predicted the optimal cut off HBV DNA level at week 48 (partial virological response) to predict virological response at week 96; a HBV DNA level of 35IU/ml (2.24 log10 copies/ml), 174 copies/ml) was found to be the most optimal cut off point to predict VR at week 96

Distribution of patients at week 96 according to optimal partial virological response (PVR) at week 48		
Optimal cut off HBV DNA* at week 48	Patients with virological response, n (%)	Patients with no virological response, n (%)
>35 IU/ml (partial virological response)	10	31 (86.1%)
<= 35 IU/ml (favourable virological response)	129 (92.8%)	5

*sensitivity was 92.8%, specificity 86.1%, positive predictive value 96.3% and negative predictive value 75.6%. Optimal cut off point was determined by the maximal Youden index (sensitivity+ specificity-1)

Patients with partial virological response (PVR) (>35 IU/ml) at week 48 showed a significantly higher risk for detectable HBV DNA levels at week 96 that those with favourable virological response at week 48 (<=35IU/ml) (OR 79.9)

E.7.8 Patients off treatment

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Wong 2004	Follow up study in a subgroup (single centre) of patients who previously participated in a RCT (5-year Lamivudine Study) and received daily lamivudine,	N=58 participated in the 5 year Lamivudine study from a single centre (original cohort). 44 patients had YMDD mutations after 5 year treatment with lamivudine. 34/58 patients who had harboured YMDD mutants for at	Chinese patients aged 16-70 years, with detectable HbsAg and HbeAg, serum HBV DNA levels of at least 5 pg/mL (as determined by solution hybridization assay) and ALT levels less than 10 times the upper limit of the normal before randomized to 5 years of treatment with lamivudine. At the end of 5 years of treatment all patients had harboured YMDD mutants for at least 2 years. Original cohort (N=58) / Year 5 cohort (N=34) Male/female: 49:9 / 25:9	-ALT>2 x ULN -HBV DNA >106 copies/ml. All prognostic factors measured at the end of 5-year lamivudine treatment.	At 4- weekly intervals for 24 weeks and then at 3-6 monthly intervals (as clinically indicated) Mean follow up=20 months after stopping lamivudine (range 7-39	ALT flare defined as ALT>= 5 x ULN together with detectable HBV DNA in the follow up after stopping lamivudine.	Glaxo Welcome Research and Development UK (GlaxoSmithkline)

	25 or 100 mg for 3 years and then open labelled lamivudine 100 mg for another 2 years.	least 2 years were followed up in this study after completing 5 year treatment with lamivudine (2 patients did not complete the 5 year lamivudine treatment, 1 patient died of ALT flare and decompensation and another emigrated, 8 patients participated in another trial of adefovir and lamivudine combination)	Median serum ALT (x ULN): 1.93 (0.57 - 9.07); 0.55 (0.31 - 4.41) Median HBV DNA (Meq/ml): 174.3 (1.8 - 822.6); 161 (<2.5 - 730) HbeAg positive: 58 (100%); 27 (79%)		months)		

Results:

7/34 patients developed ALT flare during the follow up after stopping lamivudine treatment. The peak ALT value was (5.1-14) x ULN and the peaks occurred at a median of 8 weeks (range 4-64) after stopping lamivudine treatment. All seven patients showed a return of viraemia (median 42.8 MEq/ml, range 1.3-281 MEq/ml).

Univariate analysis of factors at the end of lamivudine treatment associated with the ALT flare of hepatitis B after stopping lamivudine

Predictor factors at the end of lamivudine treatment	Number of patients (n)	ALT flare after stopping lamivudine (n,%)	P value
ALT: - <= 2 x ULN - >2 x ULN	32 2	5 (16%) 2 (100%)	0.037
HbeAg:- positive	27	6 (22%)	1

- negative	7	1 (14%)	
HBV DNA:->106 copies/ml - <=106 copies/ml	24 10	5 (21%) 2 (20%)	1

The only significant predictor for ALT flare after stopping lamivudine treatment was the ALT level at the time of stopping lamivudine therapy. The authors commented that as most (5/7) ALT flares occurred within 6 months after stopping lamivudine therapy, close monitoring in the first 6 months post treatment is essential, especially if ALT is elevated when lamivudine is stopped.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Lee 2002	Retrospective study	N= 124	Recruitment/setting: Korea Inclusion: HBeAg positive CHB patients treated with lamivudine (100mg/day). All patients were positive for serum HBsAg, HBeAg and HBV DNA over 6 months after LAM therapy. Pretreatment ALT levels were over ULN x 2 Exclusion: see above Baseline characteristics	Serum HBeAg Anti HBe HBV DNA ALT Measured every 2 or 3 months until drug discontinuation HBV DNA was measured by Digene hybrid capture II	Mean duration of LAM treatment 12.86 ± 4.44 months (range 7-30). Lamivudine was continued for an additional 2-4 months after seroconve	Relapse, defined as reappearance of serum HBV DNA and an increase in ALT at least ULN x 3 HBeAg seroconversion, defined as loss of detectable levels of HBeAg and HBV DNA in serum and appearance of anti-HBe.	Not stated

	Seroconverters (n=42)	Relapsers (n=24)	Non relapsers (n=18)
Mean age, years (SD)	36.88 ± 9.86	37.96 ± 9.81	35.44 ± 10.03
Male/female	33/9	19/5	14/4
Pretreatment HBV	342.9 ± 381.4	301.9 ± 338.4	395.5 ± 438.1

			DNA, pg/mL, mean ±SD				assay Serum hBeAg and antiHBe were measured by immunoradiometric assay kit	rsion		
			Pretreatment ALT (U/L), mean ±SD	294.5 ± 192.9	281.2 ± 161.2	305.4 ± 232.9				
			Total treatment duration (months)	12.86 ± 4.44	12.46 ± 3.56	13.39 ± 5.47				
			Additional treatment duration after seroconversion (months)	5.13 ± 3.98	6.24 ± 4.16	4.87 ± 3.48				

Results:

Median time to seroconversion was 7.76 ± 3.94 months (range 4-24).

Cumulative relapse rates at 3 and 6 months post-treatment in patients with HBeAg seroconversion were 40.5% and 57.4% respectively.

42/124 achieved HBeAg seroconversion.

HBV DNA levels at the 2nd month of treatment was not related with relapse after stopping treatment.

Table 1. The relation between virologic response and relapse within 6 months after lamivudine treatment, in patients with lamivudine induced HBeAg seroconversion

HBV DNA measured at 2nd month of treatment (N=31)			
HBV DNA thresholds (genomes/mL)	Relapse within 6 months after lamivudine treatment	Odds ratio (95% CI)*	P value**
>4.7 x 103 <4.7 x 103	10/15 (66.7%) 7/16 (43.8%)	1.524 (0.79-2.95)	0.2
>10 x 103 <10 x 103	7/12 (58.3%) 10/19 (52.6%)	1.09 (0.58-2.1)	0.76

>20 x 103 <20 x 103	5/9 (55.6%) 12/22 (54.5%)	1.02 (0.51-2.05)	0.96
>50 x 103 <50 x 103	2/4 (50%) 15/27 (55.6%)	0.9 (0.51-2.05)	0.84
HBV DNA measured at the time of seroconversion (N=42)			
HBV DNA level (genomes/mL)	Relapse within 6 months after lamivudine treatment	Odds ratio (95% CI)	P value
>4.7 x 103 <4.7 x 103	5/5 (100%) 19/37 (51.4%)	1.95 (1.42-2.67)	0.04

*OR and 95% CI were estimated using 2x2 contingency table according to HBV DNA levels.

**P value in bold denotes statistical significance

Author's conclusion: Monitoring of serum HBV DNA at the time of HBeAg seroconversion may be helpful for predicting relapse in patients with lamivudine-induced HBeAg seroconversion.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Lee 2003	Prospective follow up study	N= 49 46 patients completed succesfully the extended treatment with lamivudine	Inclusion: Patients who exhibited HbeAg loss/seroconversion during lamivudine therapy and agreed to receive extended lamivudine therapy. All patients were positive for HBeAg, HbsAg and HBV DNA and had elevated ALT levels for more than 6 months prior to lamivudine therapy. One patients achieved HbeAg loss/seroconversion on two consecutive tests during lamivudine therapy, they were allocated to either extended lamivudine therapy for 6 months or 12 months after HbeAg seroconversion. Exclusion: see above	HBV DNA levels (<200 copies/ml) Measured every 2 or 3 months until drug discontinuation HBV DNA was	Mean duration of LAM treatment 12.86 ± 4.44 months (range 7-30). Lamivudine was	Virological relapse was defined as post treatment reappearance of serum HBV DNA as measured by the DHCII assay, and/or HbeAg in two consecutive tests.	Not stated

Baseline characteristics

	Total patients (n=49)	Group 1 (n=23)	Group 2 (n=26)
Mean age, years (SD)	39.2 (11.0)	38.6 (11.0)	39.9 (11.3)
Male/female	41/8	21/2	20/6
ALT (IU/L)	146 (80-1764)	160 (80-1764)	124 (80-530)
ALT>400 IU/L	8 (16.3%)	5 (21.7%)	3 (11.5%)
HBV DNA (pg/ml)	295 (5-11748)	295 (5-11748)	265 (8-8791)
History of previous INF treatment	9 (18.4%)	2 (8.7%)	7 (26.9%)
Time to HbeAg loss (months)	4 (2-18)	3 (2-12)	4 (2-18)

Group 1: patients who received lamivudine for additional six months after HbeAg loss/seroconversion

Group 2: patients who received lamivudine for additional 12 months after HbeAg loss/seroconversion

measured by Digene hybrid capture II assay

continued for an additional 2-4 months after seroconversion

Results:

The overall cumulative post treatment relapse rates were 48% and 54% at six and 12 months follow up respectively

Most relapses (96%) occurred within 12 months after discontinuation of lamivudine and were accompanied by elevation in serum ALT levels (89%).

	Cumulative relapse rates (at 6 months) (n=22)	Cumulative non relapse rates (at 6 months) (n=24)	Positive predictive value (PPV)

HBV DNA level at time of lamivudine discontinuation (copies/mL)			
<200 (n=19)	5 (26%)	14	
200 – 1000 (n=12)	6 (50/%)	6	50%
>1000 (n=15)	11 (67%)	4 (33%)	73.3%

	Cumulative relapse rates (at 12 months) (n=25)	Cumulative non relapse rates (at 12 months) (n=21)	Positive predictive value (PPV)
HBV DNA level at time of lamivudine discontinuation (copies/mL)			
<200 (n=19)	7 (37%)	12	
200 – 1000 (n=12)	7 (58%)	5	58.3%
>1000 (n=15)	11 (73%)	4 (27%)	73.3%

Author's conclusion: Extended lamivudine for up to 12 months did not decrease the rate of post treatment virological relapse, and monitoring of serum HBV DNA by a quantitative PCR method was helpful in predicting post treatment relapse

E.7.9 Children and young people with CHb

Bibliographic reference	Study type/ Study quality	Number of patients	Patient characteristics	Prognostic factor(s)	Length of follow-up	Outcome measures	Source of funding
Nagata 1999	Retrospective study	N=22 children	Children with chronic HBV infection, selected on the basis of their response to IFN-a treatment (5MU/m2 3 times weekly for 3-12 months (median 6 months)). All were HBV DNA and HbeAg positive for at least 6 months before treatment and had minimal, mild or moderate inflammatory changes on liver biopsy. All children were negative for antibodies to hepatitis C, delta, and HIV. Baseline characteristics [ ] Total: Virological: Virological	1)HbeAg levels 2)HbeAg seroconversion 3)HbsAg levels 4)HbsAg seroconversi		Virological response to INFa defined as HBV DNA negativity and HbeAg seroconversion within 18 months of	Children's Liver Disease Foundation, Bermingham, UK

	sample (N=22)	responders (n=10)	non responders (n=12)
Median age	6 (2-14)	-	-
Sex, boys	13/22 (59%)	-	-
HBV DNA (by hybridisation), median (range)	-	66 (5-471) pg/ml	175 (2.4-800) pg/ml
HBV DNA (by PCR),median (range)	-	3.8 x 108 (4 x 106- 2 x 109)copies/ml	9 x 108 (2 x 107- 2.8 x 109) copies/ml
Mode of transmission -vertical -unkown -Rumanian adoptees		 5/10 1/10 4/10	 6/12 4/12 3/12

on 5)HBV DNA levels by hybridisation and by PCR		treatment completion.		

Results:

	Virological responders (n=10)		Virological non responders (n=12)	
Viral markers	Frequency (%)	Median time (range) to achieve viral marker in weeks	Frequency (%)	Median time to achieve viral marker in weeks
HbeAg loss	10/10 (100%)	18 (10-104)	0/12	-
HbeAg seroconversion	8/10 (80%)	12 (8-104)	0/12	-
Undetectable HBV DNA (by hybridization)	10/10 (100%)	14 (4-104)	1/12 (8.3%)	After 24 weeks treatment
HbsAg seroconversion	5/10 (50%)	12 (8-20)	0/12	-

	Number of patients with detectable HBV DNA by hybridization and quantitative PCR among

	virological responders and non virological responders during IFNa- treatment and at last follow up	
Follow up	Virological responders (n=10)	Virological non responders (n=12)
4-7 weeks Hybridisation Quantitative PCR	 -8/10 -9/10	 -12/12 -12/12
8-15 weeks Hybridisation Quantitative PCR	 -2/10 -9/10	 -12/12 -12/12
16-24 weeks Hybridisation Quantitative PCR	 -1/10 -5/10	 -12/12 -12/12
16-26 weeks Hybridisation Quantitative PCR	 -0/10 -5/10	 -11/12 -12/12

Author's conclusion:

Monitoring of HBV DNA by quantitative PCR during Interferon-a treatment may allow early prediction of response to INF-a, those this needs to be confirmed in a prospective study.

E.8 Surveillance

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Group 1	Group 2	Length of follow-up	Outcome measures	Source of funding
Kim DY, Han KH et al.	Retrospective study (abstract)	N=400	Recruitment/setting: Korea	6 monthly surveillance	12 monthly surveillance	Not applicable	Proportion (%) of patients with single nodular HCC	Not stated

Semiannual surveillance for hepatocellular carcinoma improved patient survival compared to annual surveillance (Korean experience). 2007 Hepatology; 46 (4) Suppl 1; 403A	Study quality: Inadequate information on baseline characteristics on patients Cirrhosis - unknown		Inclusion: mostly hepatitis B patients diagnosed with hepatocellular cancer by surveillance programme [ultrasound examination and alpha-fetoprotein measurement every 6 or 12 months] between May 1990 and December 2004. Exclusion: - Baseline characteristics Male:Female = 2.6:1 Group 1 (6 months), n=219 Group 2 (12 months), n=181 Mean age=57 years Aetiology of HCC: HBV, 289 (72.3%) HCV, 76 (19%) Non HBV or HCV, 32 (8%) AFP levels 109 (27.3%) had AFP ≥400ng/ml 147 (36.8%) had AFP <20ng/ml	(n=219)	(n=181)		Proportion of patients with diffuse type HCC Frequency of solitary HCC ≤3cm 5-year survival	

Results

	Group 1 (N=219)	Group 2 (N=181)	P value

	6 monthly surveillance	Annual surveillance	
% with single nodular HCC	198 (90.4%)	132 (72.9%)	<0.001
% with Diffuse type HCC	9 (4.1%)	21 (11.6%)	<0.001
% with frequency of solitary HCC ≤3cm	136 (62.1%)	93 (51.5%)	0.003
Application of curative treatments, such as resection or local ablative therapy	41 (18.7%)	22 (12.2%)	0.03
5-year survival	25%	16%	0.006 (log rank test)

Additional results:

Authors' conclusion: Semi-annual (6 monthly) surveillance resulted in the detection of HCC at an earlier stage and improved survival compared to annual surveillance in Korea.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Group 1	Group 2	Length of follow-up	Outcome measures	Source of funding
Trinchet JC and Chaffaut C et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis:a randomised trial comparing 3 and 6 month periodicities. Hepatology 2011; 54:1987-1997	Multi centre randomised trial Study quality: Only 12.5% HBV patients (indirect population) Randomisation method: computer generated using a	N=1278	Recruitment/setting: 43 sites in France and Belgium Inclusion: patients with histologically proven compensated cirrhosis (specialist liver disease centres), whatever the time of liver biopsy; a US Doppler examination was also undertaken to check inclusion and noninclusion criteria.Age	Ultrasonographic surveillance (US) every 6 months n=638 a)with alpha-fetoprotein assay (AFP) every 6 months (n=326) b)with no AFP	Ultrasonographic surveillance every 3 months n=640 a)with AFP assay every 6 months (n=328) b)with no AFP assay (n=312)	Median 47.1 months (29-65) in group 1 and 46.8 (30-66) months in	Cumulative incidence of first focal lesion at 24 and 60 months Diameter of the first lesion (mm) Cumulative incidence of HCC at 24 months and 60 months	French Ministry of Health and the French Ligue de Recherche contre le Cancer.

	permuted block with fixed block sizes of four),with trialist unaware of the block size) and 1:1 allocation ratio; with allocation concealed using a centralised phone procedure to the data management centre; stratified according to recruitment site and cirrhosis aetiology, based on a 2x2 factorial design with balanced randomisation. Sample size calculation given by authors		>18years, cirrhosis related to either excessive alcohol consumption (80g/day in males and 60g in females for at least 10 years), chronic infection with HCV or HBV, or hereditary hemochromatosis, absence of previous complications of cirrhosis (ascites, GI bleeding or HCC), patients belonging to Child Pugh class A or B and without a focal liver lesion at inclusion and written informed consent. Exclusion: patients belonging to Child Pugh class C, severe uncontrolled extrahepatic disease resulting in estimated life expectancy of <1 year, coinfection with HIV, even if controlled by an antiviral treatment.	assay (n=312) US was performed in the same centre by the same experienced operator. A standardised report was completed by each operator, mentioning the presence or not of focal liver lesions.		group 2	Survival rate at 24 and 60 months Mortality Cause of mortality	

Baseline characteristics

	US at 6 months N=638	US at 3 months N=640
Male, n (%)	438 (69.5)	445 (69.5)
Age (years), median (Q1-3)	55 (48-64)	54 (47-61)
Aetiology of cirrhosis Alcohol	 250 (39)	 252 (39.4)

HCV HBV Hemochromatosis Other*	278 (43.6) 78 (12.2) 15 (2.3) 17 (2.6)	286 (44.7) 82 (12.8) 5 (0.8) 15 (2.3)
BMI (kg/m2), median (Q1-3)	26 (23.4-29.4)	25.9 (22.9-29.1)
AST (N<40IU/L)	41 (29-72)	42 (29-68)
ALT (N<40IU/L)	38 (24-70)	37 (23-69)
GGT (N<45IU/L)	80.5 (45-161.5)	83 (44-161)
Albumin (g/L), median (Q1-3)	40 (36-43)	41 (37-44)
Alpha-fetoprotein (ng/ml), median (range)	5 (3-8)	5 (3-8.3)
Platelet count (103/mm3), median (Q1-3)	128 (89.5-165)	131.5 (93-179)
Creatinine (µm/l), median (Q1-3)	77 (68-88)	76 (65-86)

*Nonalcoholic steatohepatitis (n=15), primary biliary cirrhosis (n=2), autoimmune hepatitis (n=5), cryptogenetic cirrhosis (n=10).

After data analyses, high rates of serum AFP were found in the two groups without AFP assays (60.5% and 54.8%) (as serum AFP assays were inadequately prescribed in more than half of the patients within the non-surveillance group), which precluded reliable interpretation based on serum AFP assay randomisation. Consequently, the steering committee decided to restrict the final analysis to US randomisation only.

Compliance was estimated as inadequate in 143 (11.9%) patients – 86 (14.6%) of group 1 and 57 (9.4%) of group 2 patients.

The compliance of patients towards US surveillance was generally adequate; median interval between US examinations was 6 months (6-7) in group 1 and 3 months (3-4) in group 2.

Results

	Group 1 (n=638) US at 6 months	Group 2 (n=640) US at 3 months	P value
Follow up (months)	46 (30-66)	47 (29-65)	
Cumulative incidence of first focal lesion			

24 months 60 months	13.2% 32.8%	20.4% 35.5%	- -
Prevalence of HCC, n	70	53	
Cumulative incidence of HCC 24 months 60 months	 2.7% 12.3%	 4% 10%	 - -
Prevalence of HCC ≤3cm	70% (95%CI 59-81)	79% (95%CI 69-90%)	-
Cumulative incidence of HCC ≤3cm	9.1%	7.8%	0.48
Liver decompensation	98 (15.4%)	94 (14.7%)	0.75
Transplantation	13 (2%)	17 (2.7)%	0.58
Death N Survival rate 24 months 60 months	 82 (12.1%) 93.5% 85.8%	 72 (11.3%) 95.8% 84.9%	 0.38
Cause of death HCC Liver failure Extra hepatic cancer Bacterial infection Other	 12 (14.6%) 34 (41.5%) 7 (8.5%) 8 (9.7%) 21 (25.6%)	 17 (23.6%) 24 (33.3%) 7 (9.7%) 5 (6.9%) 19 (26.4%)	
Diameter of the first focal lesion (mm) ≤10 11-20 21-30 31-50 ≥51 Cumulative incidence of focal lesions ≤10mm in diameter 60 months	N=156 43 (28%) 78 (50%) 23 (15%) 7 (4%) 5 (3%) 28%	N=178 73 (41%) 71 (40%) 23 (13%) 7 (4%) 4 (2%) 41%	 0.002

Author's conclusion: Ultrasonographic surveillance, performed every 3 months, detects more small focal lesions than every 6 months, but does not improve detection of small HCC (fails to improve the detection rate of HCCs ≤30mm in diameter that are eligible for curate treatment), probably because of limitations in recall procedures (recommended diagnostic procedures for small focal lesions in current practice).

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Group 1	Group 2	Length of follow-up	Outcome measures	Source of funding
Santi V and Trevisani F et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. Journal of Hepatology. 2010; 53: 291-	Retrospective study Study quality: Indirect population HBV (n=59; 9.1%) 41.8% cirrhosis	N=649 HCC patients	Recruitment/setting: ITA.LI.CA centres, Italy Inclusion: HCC patients in Child-Pugh class A or B. HCC diagnosis made during a regular surveillance based on liver US, with or without alpha feto-protein determination, performed every 6 (±1 month) or 12 month (±1 month); description of presenting cancer stage available. Source of data: clinical records database between Jan 1987 to Dec 2006 at 10 medical institutions. Exclusion: Child-Pugh class c or unspecified, diagnosis of HCC made outside any surveillance, unspecified mortality of HCC diagnosis, unspecified interval of surveillance, interval outside the above mentioned ranges.	HCC detected during 6 monthly surveillance (US with or without AFP) N=510 Diagnosis and staging of HCC: the diagnosis was based on histology or cytology in 96 patients. Otherwise, diagnosis was confirmed by combining an increase (>200ng/ml) of AFP with	HCC detected during 12 monthly surveillances (US with or withour AFP) N=139	Not applicable	Median observed survival Estimated survival rates at year 1, 3 and 5 Median survival corrected for lead time *Survival was calculated from the time of cancer diagnosis to death, with values censored at the date of the last follow up and was expressed as median and 95% CI	Not stated

297				typical features of the lesion in CT or MRI or CEUS scans, or in the absence of diagnostic AFP elevation, in at least 2 techniques.				

Baseline characteristics

	Group 1 6 monthly	Group 2 12 monthly
Median age (range), year	67 (30-89)	68 (46-88)
M/F	358/152	99/40
Aetiology, n (%) HBV HCV Alcohol Multiaetiology Others	 40 (7.9) 331 (65) 39 (7.7) 77 (15.1) 22 (4.3)	 19 (13.7) 79 (56.8) 12 (8.6) 26 (18.7) 3 (2.2)
Period of diagnosis, n (%)* 1987-1996 1997-2006	 129 (25.3) 380 (74.7)	 51 (36.7) 88 (63.3)
Median ALT (ULRR), range (n=633)	1.79 (0.25-13.60)	1.50 (0.42-9.13)
Alpha feto-protein (n=631) <20ng/ml	 250 (50.3)	 65 (48.5)

21-200ng/ml	181 (36.4)	43 (32.1)
>200ng/ml	66 (13.3)	26 (19.4)
Child Pugh class, n (%)		
A	37 (73.7)	101 (72.7)
B	134 (26.3)	38 (27.3)
Cancer stage**		
Solitary ≤2cm, V0, N0, M0	120 (24.1)	7 (5.1)
Solitary 2.1-3cm, V0,N0,M0	94 (18.9)	22 (16.1)
Solitary 3.1-5cm, V0,N0,M0	61 (12.3)	30 (21.9)
2-3 nodules, ≤3cm, V0,N0,M0	73 (14.7)	20 (14.6)
Outside Milano criteria	149 (30)	58 (42.3)
Median tumour size (cm), range**	2.5 (0.2-18)	3.3 (0.8-11)
Treatments, n (%)***		
Transplantation	18 (3.6)	4 (3)
Resection	59 (11.7)	19 (14.1)
Percutaneous ablation	164 (32.4)	36 (26.7)
TACE	173 (34.2)	35 (25.9)
Others/palliative	92 (18.2)	41 (30.4)

*p=0.01

**p=<0.001

***p=0.01

Cirrhosis was histologically confirmed in 271 patients

The median duration of surveillance was 10 years (0.5-42) in group 1 (n=381 or 74.7) and 9 years (1-40) in group 2 (n=94 or 67.6%)

Results

Survival

Data on follow up were available in 508 (99.6%) patients of group 1 and in all group 2 patients.

Mean follow up after HCC diagnosis was 38.6±32.8 months and 522 (80.4%) patients died during the follow up.

	Group 1	Group 2	P value

Median observed survival (months) (95%CI)	45 (40-50)	30 (24-36)	0.001
Estimated survival rate Year 1 3 5	 85.4% 80.6% 57.2%	 40.1% 37.5% 21.1%	 - - -
Median observed survival, corrected for lead time * (months) (95%CI)	40.3 (34.9-45.7)	-	0.028**
Estimated survival rate, corrected for lead time Year 1 3 5 	 78.5% 54.1% 34.3%	 - - -	

*the calculated lead time was 141 days.

**the observed survival corrected for lead time in group 1 was significantly higher than those regarding the observed survival of group 2.

Univariate and multivariate analysis for the detection of a HCC beyond the very early stage (solitary nodule >2cm or multinodular tumour with/without vascular invasion and/or metastases)

	Univariate analysis P value	Multivariate analysis Odds ratio (95%CI)
Surveillance Semiannual (6 monthly) Annual (12 monthly)	 <0.001 	 1.0 5.99 (2.57-13.98)
Alpha feto-protein ≤20 ng/ml 21-200ng/ml >200ng/ml	0.091 	 1 0.91 (0.59-1.41) 2.58 (1.17-5.69)

*adjusted for age, platelet count, AFP, Child-Pugh class and esophageal varices.

Univariate and multivariate analysis looking at variables associated with mortality

	Univariate analysis P value	Multivariate* analysis hazard ratio (95%CI)
Surveillance Semiannual (6 monthly) Annual (12 monthly)	0.028	 1 1.39 (1.05-1.82)
Alpha feto-protein ≤20 ng/ml 21-200ng/ml >200ng/ml	<0.001	 1 1.32 (1.03-1.70) 1.77 (1.27-2.46)

*model adjusted for age, platelet count, AFP, C-P class, cancer stage and all treatments other than OLT.

Potential limitations: selection bias, determined by the subjective choice of the interval. Doctors tend to shorten the interval in patients that are likely at very high risk of HCC, e.g. those with an elevated baseline AFP. And this would result in an increased number of higher risk patients submitted to a semi-annual surveillance.

Author's conclusion: Semiannual surveillance increases the detection rate of very early hepatocellular carcinomas and reduces the number of advanced tumours as compared to the annual program.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Group 1	Group 2	Length of follow-up	Outcome measures	Source of funding
Wang JH and Chang KC et al. 2011. Hepatocellular carcinoma surveillance with 4 versus 12 months	Prospective study (random sampling) (abstract) Study quality: Proportion of HBV and HCV unclear % Cirrhosis -	N=744	Recruitment/setting: residents of 10 townships, Taiwan; they were invited to the study by mail and phone call. Inclusion: patients with HBV and HCV, platelet count ≤150 (x109)/L, positive HBsAg or antibody to HCV Exclusion: -	HCC surveillance (US + AFP) every 4 months (n=387) A total of 12 residents (both	HCC surveillances (US + AFP) every 12 months (n=357)	Not applicable	HCC Cumulative 3 year HCC incidence Cumulative 4-year survival rate Tumour size ≤2cm	Not stated

interval for patients with chronic viral hepatitis – a randomised community study	unclear		Baseline characteristics – not given	groups) were excluded due to presence of HCC, newly diagnosed HCC and decline to participate study/ entrance visit US.				

Results

Outcome	Group 1 4 monthly surveillance (n=387)	Group 2 12 monthly surveillance (n=357)	P value
HCC, n	24	15	
Cumulative 3 year HCC incidence	11.7%	9.7%	0.198
Tumour size ≤2cm	-	-	0.003*
Mean tumour size (SD), cm	1.9 (0.7	2.9 (1.5)	0.006
Cumulative 4 year survival rate	45.3%	42.7%	0.38

*group 1 significantly had more patients with tumour size ≤2cm, than group 2 patients.

Author's conclusion: Compared with 12 months interval for HCC surveillance, 4 months interval US surveillance detected more patients in tumour size ≤2cm, in BCLC very early stage and fit for curate treatments. However, there was no significant difference in survival up to 4 years follow up between two groups.

Reference	Study type/ Study quality	Number of patients	Patient characteristics	Group 1	Group 2	Length of follow-up	Outcome measures	Source of funding

	Prospective study (random sampling) (abstract) Study quality: Inadequate information on recruitment	N=	Recruitment/setting: Source of data: Exclusion: Baseline characteristics Mean age, years: 46 Duration worked at GP, years (range): 14 (1-35) Practice contains >5,000 patients, %: 96%			Not applicable		Not stated

Results

Outcome	n/N (%)

Author's conclusion:

Appendix F: Economic evidence tables

F.1 Antiviral therapies

F.1.1 Monotherapies

Spackman DE, Veenstra DL. A cost-effectiveness analysis of currently approved treatments for HBeAg-positive chronic hepatitis B. Pharmacoeconomics. 2008; 26(11):937-949. Ref ID: SPACKMAN2008

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision model **Approach to analysis:** Markov model with 14 hepatitis B and liver disease health states used to extrapolate long-term outcomes (life expectancy and quality adjusted life expectancy) and costs based on short-term outcomes (HBeAg seroconversion and ALT normalisation) from a systematic review. **Perspective:** US third party payer **Time horizon:** lifetime **Treatment effect**	**Population:** Non-cirrhotic patients with HBeAg positive chronic hepatitis B (HBV DNA positive, elevated ALT) **Cohort settings:** HBeAg positive = 100% Start age = 35 years **Interventions:** 1. No treatment 2. Adefovir 3. Lamivudine 4. Telbivudine 5. Peg INF α 6. Entecavir Follow-up therapy was adefovir for all treatments except adefovir and peg INF, for which follow-up therapy was entecavir.	**Total costs (mean per patient):** 1. £17,917 2. £33,198 3. £29,529 4. £34,288 5. £34,201 6. £32,143 **Currency & cost year:** 2008 US dollars (presented here as 2008 UK pounds‡) **Cost components incorporated:** Direct medical costs: drug costs, costs related to management of CHB, viral flares, compensated and decompensated cirrhosis, HCC, liver transplantation. Assumption that there was no difference in physician visits or laboratory monitoring between drugs.	**Primary outcome measure:** QALYs (mean per patient) 1. 17.88 2. 18.25 3. 18.38 4. 18.55 5. 18.64 6. 18.70	**Primary ICER (Intvn 6 vs Intvn 1):** ICER: £17,350 per QALY gained Probability most cost-effective: 57% at WTP of £32k per QALY Adefovir, lamivudine, telbivudine and peg INF α dominated or extendedly dominated by entecavir Probability Peg INF α most cost-effective: 37% at WTP of £32k per QALY **Analysis of uncertainty:** Results were sensitive to deterministic sensitivity analysis around variables: • Seroconversion rates with entecavir in years 2-4 • seroconversion rates in years 3-4 in patients treated first with peg INF and then entecavir • Decreasing RR of cirrhosis associated with entecavir after peg INF At extremes, these variable made peg INF more effective and potentially cost-effective.

duration: 4 years **Discounting:** Costs = 3%; Outcomes = 3%				Entecavir was more cost-effective when viral suppression decreased the risk of cirrhosis for all years of treatment not just first year. Entecavir was not cost-effective when the baseline seroconversion rate for no treatment increased.

Data sources

Health outcomes: Transitions through the model were based on spontaneous or treatment-induced response (defined as HBeAg seroconversion), relapse and development of treatment resistance with or without a severe hepatic flare. Key clinical events came in progression from chronic hepatitis B to active cirrhosis, from which patients could progress to decompensated cirrhosis, and liver transplantation. HBeAg seroconverted patients could develop inactive cirrhosis, which was associated with a lower risk of decompensation than active cirrhosis. All patients were assumed to be at risk for hepatocellular carcinoma (HCC) except those who had received a liver transplant.

Response rates taken from a non-systematic review of the available literature. Absolute estimates of response from Chang 2006[19], Marcellin 2003[22], Lai 2007[20] and Lau 2005[21] were adjusted slightly and used to parameterise effects after one year of treatment. Absolute estimates of response after year two of treatment were taken from a variety of sources and adjusted based on loss to follow-up and cumulative incidence figures. For response rates at years three and four, the same figure (13%) was applied to all treatments.

Resistance rates were taken from a non-systematic review of the literature. Absolute estimates of resistance were taken from several conference abstracts (Tenney 2006; Han 2007; Qi 2004) and two other studies (Lai 2007[20]; Lin 1999) and adjusted based on loss to follow-up and cumulative incidence figures.

Durability of seroconversion was assumed to be 80% for all antiviral therapies, following the use of 6-month consolidation therapy (continuation of treatment beyond the point at which seroconversion is achieved). These figures were based on RCT data from Chang 2007[19], [22], Lai 2007[20]. Consolidation therapy is not appropriate for treatment with pegylated interferon, but the durability of response for pegylated interferon was estimated at 82% in the 6 months following end of 12 months of treatment.

The authors assumed that patients who achieved undetectable levels of HBV DNA but did not seroconvert had a decreased risk of cirrhosis in the first year of treatment. These estimates were calculated using the proportion of patients who achieved viral elimination and the average viral load of those who did not to the baseline risk of cirrhosis of 4.4%. This method resulted in the following relative risk reductions compared to the baseline risk of cirrhosis: adefovir 0.77; entecavir 0.13; lamivudine 0.51; pegylated interferon 0.95; telbivudine 0.17.

Quality-of-life weights: Most health state utilities were derived from a study of 100 individuals from the US general population using the standard gamble technique. The utility for HBeAg seroconversion was obtained from a previous economic evaluation by Wong and colleagues[32]. Utilities for uncomplicated resistance and non-replicating

cirrhosis were assumed to be the same as for the chronic hepatitis B state and patients with a flare were assigned a utility decrement equivalent to 1 month of decompensated cirrhosis. Because of the significant adverse effects associated with pegylated interferon treatment, a disutility of 0.05 was applied to time spent undergoing this treatment[12].

Cost sources: The majority of annual direct medical costs were obtained from a retrospective cohort study by Lee at al using healthcare claims data from large US managed care organisations. Health state costs were taken from a variety of sources, mainly previously published cost-effectiveness analyses[7,32,33]. Drug costs were obtained from the 2007 wholesale acquisition cost. The authors made the assumption that there was no difference in physician visits or laboratory monitoring between drugs.

Comments

Source of funding: The study was supported by an unrestricted grant from Bristol-Meyers Squibb, makers of entecavir.

Limitations: The study includes most, but not all comparators relevant to the review question (e.g. tenofovir is missing); treatment duration is a maximum of 4 years, whereas in practice people may go on to receive treatment with alternative drugs; costing perspective is US third-party payer, thus some uncertainty about applicability of US unit costs and estimates of resource use; costs and effects discounted at 3% per annum (3.5% preferred by NICE); changes in health-related quality of life estimated by general US population, not directly from patients/carers; no health state to capture most important outcome of HBsAg loss; unclear how closely treatment effect estimates match the NCGC clinical review; unclear whether estimates of cost and resource use are from best available sources; potential conflict of interest (funded by Bristol Meyers Squibb, makers of entecavir)

Other:

Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

Abbreviations: CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; ‡ Converted using 2008 Purchasing Power Parities [34]
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

Buti M, Brosa M, Casado MA et al. Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B. J Hepatol. 2009; 51(4):640-646. Ref ID: BUTI2009

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision model **Approach to analysis:** Markov model of one-	**Population:** Patients with HBeAg-positive or HBeAg-negative chronic hepatitis B **Cohort settings:** Start age = 40 years	**Total costs (mean per patient):** HBeAg Positive 1. 74,138 2. 77,452 3. 81,066 4. 80,242	**Primary outcome measure:** QALYs (mean per patient) HBeAg Positive 1. 13.69 2. 14.67 3. 14.68	**Primary ICERs: Cost per QALY gained** **HBeAg Positive** Tenofovir: £2,150 compared to no treatment Adefovir, entecavir and telbivudine are dominated by tenofovir. Lamivudine is extendedly dominated by tenofovir.

year cycles to evaluate the probability of suffering from different disease complications from patients with virologic response or non-response. **Perspective:** Spanish NHS **Time horizon:** lifetime **Treatment effect duration:** (e.g. 5 yrs) **Discounting:** Costs = 3%; Outcomes = 3%	**Interventions:** 1. No treatment 2. Lamivudine (100 mg/day) 3. Adefovir (10 mg/day) 4. Entecavir (0.5 mg/day) 5. Telbivudine (600 mg/day) 6. Tenofovir (300 mg/day) For HBeAg positive patients, therapy was administered until 6 months after HBeAg seroconversion. For HBeAg negative patients, therapy was considered indefinite.	5. 80,641 6. 77,880 HBeAg Negative 1. 80,770 2. 84,930 3. 92,370 4. 102,194 5. 98,753 6. 94,123 **Currency & cost year:** 2008 Spanish Euros (presented here as 2008 UK pounds‡) **Cost components incorporated:** Direct medical costs – diagnosis, laboratory testing, drugs, follow-up, disease complication costs.	4. 15.21 5. 14.96 6. 15.43 Incremental (2-1): (CI , ; p=NR) HBeAg Negative 1. 12.48 2. 14.30 3. 14.21 4. 16.11 5. 15.47 6. 16.28 **Other outcome measures:** Life years (mean): HBeAg Positive 1. 16.70 2. 17.65 3. 17.67 4. 18.18 5. 17.94 6. 18.39 HBeAg Negative 1. 15.69 2. 17.44 3. 17.36 4. 19.13	**HBeAg Negative** Lamivudine: £2,286 compared to no treatment Tenofovir: £4,643 compared to lamivudine Adefovir is dominated by lamivudine and entecavir and telbivudine are dominated by tenofovir. **Other: Cost per life year gained** **HBeAg Positive** Tenofovir: £2,214 compared to no treatment **HBeAg Negative** Lamivudine: £2,378 compared to no treatment Tenofovir: £4,996 compared to lamivudine **Analysis of uncertainty:** **HBeAg-positive** • In the base case, adefovir + lamivudine was used as the salvage therapy. In a sensitivity analysis, tenofovir+entecavir was used as salvage therapy. This increased both costs and QALYs, but did not change the incremental results. • Results of the probabilistic analysis were presented in a pairwise fashion, e.g. each drug compared to tenofovir. Results of these pairwise comparisons show that tenofovir dominates adefovir, entecavir and telbivudine in 100% of simulations and dominates lamivudine and no treatment in

			5. 18.53 6. 19.28	56% and 14% respectively. **HBeAg-negative** • Results of the probabilistic analysis were presented in a pairwise fashion, e.g. each drug compared to tenofovir. Results of these pairwise comparisons show that tenofovir dominates lamivudine in 1%; adefovir in 44%, entecavir in 90%; telbivudine in 98%; no treatment in 2% of simulations.

Data sources

Health outcomes: Treatment response and HBV drug resistance rates for each strategy were obtained from published studies[19,20,25-27,30,35-37], some of which are included in the NCGC clinical review and some of which are not.

Quality-of-life weights: Utility figures obtained by Herdman and colleagues for a Spanish population were assigned to the model health states.

Cost sources: Drug costs were taken from the Medicine database of the General Council of Pharmacists Official College. Complication costs were taken from a previously published burden of illness study by Idris and colleagues and updated using current clinical practices and obtained from expert opinions.

Comments

Source of funding: The study was supported in part by a research grant from Gilead Sciences, makers of adefovir and tenofovir

Limitations: The study includes most, but not all comparators relevant to the review question (e.g. pegylated interferon is missing); costing perspective is Spanish NHS, thus some uncertainty about applicability of Spanish unit costs and estimates of resource use; costs and effects discounted at 3% per annum (3.5% preferred by NICE); changes in health-related quality of life estimated for Spanish population, and therefore may be different from UK values; no health state to capture most important outcome of HBsAg loss; unclear how closely treatment effect estimates match the NCGC clinical review; unclear whether estimates of cost and resource use are from best available sources; potential conflict of interest (funded by Gilead Sciences, makers of adefovir and tenofovir)

Other:

Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

*Abbreviations: CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; ‡ Converted using 2008 Purchasing Power Parities [34] * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

Veenstra DL, Spackman DE, Bisceglie A et al. Evaluating anti-viral drug selection and treatment duration in HBeAg-negative chronic hepatitis B: a cost-effectiveness analysis. Aliment Pharmacol Ther. 2008; 27(12):1240-1252. Ref ID: VEENSTRA2008A				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision model **Approach to analysis:** 15-state Markov model of annual cycles to evaluate the probability of response and development of resistance to treatment and reduction in disease progression and death. **Perspective:** US third party payer **Time horizon:** lifetime **Treatment effect duration:** different durations compared **Discounting:** Costs = 3%; Outcomes = 3%	**Population:** Non-cirrhotic patients with HBeAg-negative chronic hepatitis B (HBV DNA positive and elevated ALT) **Cohort settings:** Start age = 44 years **Interventions:** 1. Lamivudine 5 years 2. Lamivudine 10 years 3. Lamivudine lifetime 4. Lamivudine 5 years on – 1 year off 5. Adefovir 5 years 6. Adefovir 10 years 7. Adefovir lifetime 8. Adefovir 5 on-1off 9. Entecavir 5 years 10. Entecavir 10 years 11. Entecavir lifetime 12. Entecavir 5 on-1 off	**Total costs (mean per patient):** 1. 29,685 2. 45,565 3. 95,381 4. 73,474 5. 37,655 6. 54,508 7. 113,924 8. 88,163 9. 36,213 10. 51,344 11. 97,403 12. 73,958 **Currency & cost year:** 2006 US dollars (presented here as 2006 UK pounds‡) **Cost components incorporated:** Direct medical costs: drug costs, costs related to management of CHB, viral flares, compensated and	**Primary outcome measure:** QALYs (mean per patient) 1. 16.07 2. 16.99 3. 18.83 4. 18.49 5. 15.85 6. 16.69 7. 18.42 8. 18.00 9. 16.71 10.17.59 11.19.46 12.19.21	**Incremental analysis (ICERs):** Lamivudine 5 yrs = least cost Entecavir 5 yrs = £10,200 Entecavir 5 on-1off = £15,098 Entecavir lifetime = £93,779 All adefovir strategies dominated Probability cost-effective at WTP $30k: Entecavir 5 on-1 off = 99% **Analysis of uncertainty:** Results were sensitive to the following variables: • rate of resistance with lamivudine • baseline risk of cirrhosis • cost of entecavir • response to salvage therapy When durability of response was decreased (i.e. risk of relapse increased), then strategies involving cessation of therapy increased costs and reduced QALYs. Only when risk of relapse was 90%, lifetime treatment with adefovir was more effective than 5 on-1 off treatment with lamivudine.

	Patients who developed resistance had adefovir or entecavir added to treatment (unclear who had which or why)	decompensated cirrhosis, HCC, liver transplantation. Assumption that there was no difference in monitoring costs		

Data sources

Health outcomes: Transitions through the model were based on treatment-induced response (defined as undetectable HBV DNA), relapse, HBsAg loss and development of treatment resistance with or without a severe hepatic flare. Key clinical events came in progression from chronic hepatitis B to active cirrhosis, from which patients could progress to decompensated cirrhosis, and liver transplantation. Patients who had achieved a response could develop inactive cirrhosis, which was associated with a lower risk of decompensation than active cirrhosis. All patients were assumed to be at risk for hepatocellular carcinoma (HCC) except those who had experienced HBsAg loss or received a liver transplant.

Estimates for baseline risk of disease progression associated with no treatment were taken from a variety of sources including Hsu 2002, Iloeje 2006, Fattovich 2002, Chen 2006, Lai 2006, Hadziyannis 2006, McMahon 2001, Kim 2004 and from a computer simulation model of the natural history of hepatitis B infection developed by Kim and colleagues (presented only in abstract form). The authors have estimated that the annual risk of progressing to compensated cirrhosis from HBeAg-negative chronic hepatitis B is 2.9%, nearly 70% less than the same annual risk for patients with HBeAg-positive disease.

The authors assumed that patients remaining in the cirrhosis state without progression to decompensation or HCC had the same mortality risk as the general population in the US given that the clinical events that lead to premature death for these patients is captured as part of transitions from decompensated cirrhosis and HCC health states. The annual probability of liver transplant for a decompensated patient was 2.6% based on a retrospective analysis of a national organ transplant database (Kim 2004).

Response rates taken from a non-systematic review of the available literature. Absolute estimates of response in the first year of treatment were taken from Lai 2006 (entecavir vs lamivudine) and Hadziyannis 2003 (adefovir). Absolute estimates of response in the second year were taken from Hadziyannis 2005 and a conference abstract by Lai (2006). Estimates of treatment durability after cessation of therapy were informed by a variety of studies[23,25,29], with 70% relapse being the final figure used for all drugs.

Resistance rates were taken from a non-systematic review of the literature. Absolute estimates of resistance were taken from a variety of sources: Colonno 2006 for entecavir (0% in years 1-2; 1% in years 3+); Lai 2006 and DiMarco 2004 for lamivudine (6% in year 1; 25% in years 2+); Hadziyannis 2003 and Hadziyannis 2006 for adefovir (0% in year 1; 5% in years 2+).

Response rates for patients who go on to receive salvage combination therapy with lamivudine+adefovir were informed by data from Lampertico 2005, Rapti 2007[38] and

Vassiliadis 2005[39]. The authors made the assumption that there was no resistance with combination salvage therapy.

Quality-of-life weights: Health state utility estimates were derived from a study by Levy and colleagues of 100 individuals from the US general population using the standard gamble technique. The utility for achieving a response (undetectable HBV DNA) was obtained from a previous economic evaluation among HBeAg-positive patients by Wong and colleagues[32]. It is not stated in the text, but it is assumed that the authors have equated the utility attached to the achievement of undetectable HBV DNA in patients with HBeAg-negative disease with that of achieving seroconversion in patients with HBeAg-positive disease. The same utility was attached to HBsAg seroconversion. Patients experiencing a flare due to drug resistance were assigned a utility decrement equivalent to 1 month of decompensated cirrhosis.

Cost sources: The majority of annual direct medical costs were obtained from a retrospective cohort study by Lee at al using healthcare claims data from large US managed care organisations. Health state costs were taken from a variety of sources, mainly previously published cost-effectiveness analyses[7,32,33]. Drug costs were obtained from the 2007 wholesale acquisition cost. The authors made the assumption that there was no difference in physician visits or laboratory monitoring between drugs.

Comments

Source of funding: The study was funded in full by an unrestricted grant from Bristol-Meyers Squibb, makers of entecavir.

Limitations: The study includes most, but not all comparators relevant to the review question (e.g. tenofovir, telbivudine and pegylated interferon are missing); costing perspective is US third-party payer, thus some uncertainty about applicability of US unit costs and estimates of resource use; costs and effects discounted at 3% per annum (3.5% preferred by NICE); changes in health-related quality of life estimated by general US population, not directly from patients/carers; unclear how closely treatment effect estimates match the NCGC clinical review; unclear whether estimates of cost and resource use are from best available sources; potential conflict of interest (funded by Bristol Meyers Squibb, makers of entecavir)

Other:

Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

Abbreviations: CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; ‡ Converted using 2006 Purchasing Power Parities [34]
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious Limitations / Very serious limitations*

F.1.2 Combinations

Veenstra DL, Sullivan SD, Clarke L et al. Cost effectiveness of entecavir versus lamivudine with adefovir salvage in HBeAg-positive chronic hepatitis B. Pharmacoeconomics. 2007; 25(11):963-977. Ref ID: VEENSTRA2007

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision model **Approach to analysis:** Markov model with 14 hepatitis B and liver disease health states used to extrapolate long-term outcomes (life expectancy and quality adjusted life expectancy) and costs based on short-term outcomes (HBeAg seroconversion and ALT normalisation) from a systematic review. **Perspective:** US third party payer **Time horizon:** lifetime **Treatment effect duration:** drug dependent **Discounting:** Costs = 3% ; Outcomes = 3%	**Population:** Non-cirrhotic patients with HBeAg positive chronic hepatitis B (HBV DNA positive, elevated ALT) **Cohort settings:** Start age = 35 years M = NR **Intervention 1:** Entecavir (0.5 mg/day, 2 years) with addition of adefovir as salvage for 1 year **Intervention 2:** Lamivudine (100 mg/day, 2 years) with addition of adefovir as salvage for 1 year **Intervention 3:** Adefovir+lamivudine (10 mg/day and 100 mg/day, respectively, 2 years)	**Total costs (mean per patient):** Intvn 1: £22,948 Intvn 2: £21,568 Intvn 3: £23,825 **Currency & cost year:** 2006 US dollars (presented here as 2006 UK pounds‡) **Cost components incorporated:** Direct medical costs: drug costs, costs related to management of CHB, viral flares, compensated and decompensated cirrhosis, HCC, liver transplantation. Assumption that there was no difference in physician visits or laboratory monitoring between drugs.	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: 18.55 Intvn 2: 18.27 Intvn 3: 18.32	**Primary ICER (Intvn 2 vs Intvn 1):** Entecavir dominates both other strategies – lamivudine and lamivudine+adefovir **Subgroup analyses:** NR **Analysis of uncertainty:** The comparison of combination treatment was conducted as part of sensitivity analysis, therefore the other sensitivity analyses are not applicable.

Data sources
Health outcomes: Transitions through the model were based on spontaneous or treatment-induced response (defined as HBeAg seroconversion), relapse and development of treatment resistance with or without a severe hepatic flare. Key clinical events came in progression from chronic hepatitis B to active cirrhosis, from which patients could progress to decompensated cirrhosis, and liver transplantation. HBeAg seroconverted patients could develop inactive cirrhosis, which was associated with a lower risk of decompensation than active cirrhosis. All patients were assumed to be at risk for hepatocellular carcinoma (HCC) except those who had received a liver transplant. Key model assumptions included: • Patients who achieved HBeAg seroconversion due to treatment had the same course of disease as patients who spontaneously seroconverted. • Patients who partially responded (defined as decrease in viral load to <700,000 copies/mL without HBeAg seroconversion) at the end of year 1 continued on therapy in year 2. • Non-responders (defined as having a viral load >700,000 copies/mL) to entecavir at the end of year 1 were continued for year 2 but received no benefit. Non-responders to lamivudine at the end of year 1 had adefovir added to therapy. • Patients who did not seroconvert but achieved complete viral suppression in year 1 and continued therapy had a reduced risk of cirrhosis in year 2. • Patients who did not respond to treatment, once off treatment, had the same disease progression and spontaneous seroconversion rates as untreated patients (i.e. followed natural history of disease). Baseline risk estimates of spontaneous seroconversion were taken from Marcellin 2003[8], Yuen 2003, McMahon 2001, Lok 1987, Lai 1998[9] and Dienstag 1999[10]. Baseline risk estimates for progression to cirrhosis were informed by data from Liaw 1988, Lin 1999 and other cost-effectiveness analyses[11-15]. Baseline risk estimates for progression from compensated to decompensated cirrhosis were taken from Fattovich 2002. Response rates taken from a non-systematic review of the available literature. Absolute estimates of response at end of year 1 from Chang 2006[3], at end of year 2 from Gish 2005 (conference abstract), • Year 1 o Seroconversion: 21% for entecavir; 18% for lamivudine o HBV DNA clearance: 67% for entecavir; 36% for lamivudine o Partial response: 70% for entecavir; 46% for lamivudine o Non-responders: 5.4% for entecavir; 26.4% for lamivudine • Year 2 o Seroconversion: 12.9% for entecavir; 13.3% for lamivudine (clinical trial data adjusted for loss to follow-up)

Seroconversion rates for salvage therapy were taken from Perrillo and colleagues[4] and put at 8% at the end of year 1. The authors do not report estimates of seroconversion for the combination lamivudine and adefovir strategy. They simply state that the estimates come from Sung et al 2003 (conference abstract) and that compared with lamivudine therapy alone, the combination resulted in a similar viral suppression and HBeAg loss, a decrease in the proportion of patients achieving normalisation of ALT and a reduction in the incidence of lamivudine resistance from 20% to 2%.

Resistance rates were taken from a non-systematic review of the literature. No drug resistance has been detected in entecavir treated patients after 2 years of treatment and 'preliminary evidence' suggests that resistance is 1.1% after 3 years of therapy. Based on this, the authors assume 0% resistance in years 1 and 2. Drug resistance for lamivudine was estimated at 23% annually, based on an evaluation of open label studies by Lok and colleagues[16].

Based on evidence from Chang et al[3] and Iloeje et al (2006), treatment induced viral suppression was assumed to reduce the risk of cirrhosis during the first year of treatment (0.6% for entecavir; 2.2% for lamivudine). Non-seroconverted patients were assumed to return to baseline 4.4% risk of cirrhosis after the first year of treatment, even if they continued therapy.

Durability of seroconversion was assumed to be 71% for all entecavir and 69% for lamivudine. These figures were based on RCT data from Gish 2005 (conference abstract) but are not explained in the text.

Quality-of-life weights: Most health state utilities were based on the results of a study by Levy et al 2005 (conference abstract). The utility for HBeAg and HBsAg seroconversion was obtained from a previous economic evaluation by Wong and colleagues[15]. Utilities for uncomplicated resistance and non-replicating cirrhosis were assumed to be the same as for the chronic hepatitis B state and patients with a flare were assigned a utility decrement equivalent to 1 month of decompensated cirrhosis.

Cost sources: The majority of annual direct medical costs were obtained from a retrospective cohort study by Lee at al using healthcare claims data from large US managed care organisations. Health state costs were taken from a variety of sources, mainly previously published cost-effectiveness analyses[11,12,15]. Drug costs were obtained from the 2007 wholesale acquisition cost. The authors made the assumption that there was no difference in physician visits or laboratory monitoring between drugs.

Comments

Source of funding: Bristol Myers Squibb, makers of entecavir

Limitations: The study does not include all comparators of interest, and only includes the combination lamivudine and adefovir as an initial treatment in a sensitivity analysis; treatment duration is a maximum of 2 years, whereas in practice people may go on to receive treatment with alternative drugs; costing perspective is US third-party payer, thus some uncertainty about applicability of US unit costs and estimates of resource use; costs and effects discounted at 3% per annum (3.5% preferred by NICE); unclear how closely treatment effect estimates match the NCGC clinical review; unclear whether estimates of cost and resource use are from best available sources; potential conflict of interest (funded by Bristol Meyers Squibb, makers of entecavir)

Other:

Overall applicability*: Partially applicable Overall quality: Very serious limitations**

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years
‡ Converted using 2006 Purchasing Power Parities[17]
** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value in Health. 2010; 13(8):922-933. Ref ID: DAKIN2010A

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision model **Approach to analysis:** Markov model used to model progression of CHB, costs and benefits of NA treatment, accounting for drug resistance and effect in HBeAg positive and negative CHB **Perspective:** UK NHS **Time horizon:** lifetime (42 years) **Treatment effect duration:** dependent on durability of response **Discounting:** Costs =	**Population:** A heterogenous cohort of nucleos(t)ide-naïve adults with compensated CHB, deterctable HBV DNA and evidence of active liver disease for whom NA therapy was considered appropriate • 5.3% were cirrhotic and of these 50% were HBeAg negative CHB • 94.7% were non-cirrhotic and of these 55.5% were HBeAg negative. **Cohort settings:** Start age = 38 years M = 63% **Interventions:** 211 sequences of up to 3 NAs or combinations followed by best supportive care were	**Total costs (mean per patient):** TDF then TDF+LAM: £40,610 ADV+LAM then TDF+LAM: £54,735 ENT+ADV then LAM: £88,206 **Currency & cost year:** 2006/07 UK pounds **Cost components incorporated:** drugs, consultations, compensated and decompensated cirrhosis, HCC (including liver transplant),	**Primary outcome measure:** QALYs (mean per patient) TDF then TDF+LAM: 11.19 ADV+LAM then TDF+LAM: 10.78 ENT+ADV then LAM: 11.09 **Other outcome measures (mean):** NR	**Primary ICER (Intvn 2 vs Intvn 1):** ICER: TDF then TDF+LAM dominates both other interventions CI: NR Probability cost-effective: NR **Other:** NR **Subgroup analyses:** NR **Analysis of uncertainty:** Results for the first line combination treatments were presented only as total costs and QALYs for the base case with no further detail provided in sensitivity analysis.

3.5%; Outcomes = 3.5%	evaluated, but only the 20 most cost-effective of the main options were presented in the article. Note: Only presenting comparisons relevant to review in this extraction.			

Data sources

Health outcomes: transition probabilities from a network meta-analysis{Dakin, 2010 DAKIN2010 /id}

Quality-of-life weights: Health state utilities for most disease states were based on standard gamble valuations of each health state from a study of UK CHB patients[18]. Quality of life of HBsAg-seroconverted patients was based on UK population norms from Kind et al 1998. Quality of life of patients in the HBeAg-seroconverted state was assumed to be 1% lower than population norms, based on a previous economic evaluation[15].

Cost sources: Estimates of resource use and cost for managing severe liver disease were based on a large, retrospective UK microcosting study of patients with chronic hepatitis C. The assumption was made that these costs were unlikely to differ between patients with hepatitis C and hepatitis B. The cost of managing patients in other disease states was based on clinical estimates of frequency of outpatient consultations for each patient group and the tests that would be performed at each consultation. Unclear as to whether these represent the best available estimates.

Comments

Source of funding: Gilead Sciences, makers of tenofovir

Limitations: Study population is appropriate and may be reflective of the case mix seen in clinical practice, but difficult to know if therapies are more, less or equally cost-effective in both HBeAg positive and negative and with and without compensated cirrhosis; unclear how closely effect estimates match the clinical evidence review; estimates of resource use associated with severe liver disease taken from costing study among hepatitis C patients; potential conflict of interest.

Overall applicability*: Minor limitations **Overall quality**:** Directly applicable

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

F.1.3 Sequential therapies

Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value in Health. 2010; 13(8):922-933. Ref ID: DAKIN2010A				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision model **Approach to analysis:** Markov model used to model progression of CHB, costs and benefits of NA treatment, accounting for drug resistance and effect in HBeAg positive and negative CHB **Perspective:** UK NHS **Time horizon:** lifetime (42 years) **Treatment effect duration:** dependent on durability of response **Discounting:** Costs = 3.5%; Outcomes = 3.5%	**Population:** A heterogeneous cohort of nucleos(t)ide-naïve adults with compensated CHB, detectable HBV DNA and evidence of active liver disease for whom NA therapy was considered appropriate • 5.3% were cirrhotic and of these 50% were HBeAg negative CHB • 94.7% were non-cirrhotic and of these 55.5% were HBeAg negative. **Cohort settings:** Start age = 38 years M = 63% **Interventions:** 211 sequences of up to 3 NAs or combinations followed by best supportive care were evaluated, but only the 20 most cost-effective of the main options were presented in the article.	**Total costs (mean per patient):** 1. £11,189 2. £14,877 3. £30,614 4. £39,914 5. £40,610 6. £40,612 7. £39,844 8. £40,268 9. £28,915 10. £31,129 11. £40,771 12. £38,744 13. £43,624 14. £45,327 15. £47,878 16. £49,071 17. £52,082 18. £53,429 19. £54,735 20. £88,206 **Currency & cost year:** 2006/07 UK pounds	**Primary outcome measure:** QALYs (mean per patient) 1. 9.18 2. 9.56 3. 10.68 4. 11.17 5. 11.19 6. 11.19 7. 11.16 8. 11.17 9. 9.87 10. 10.27 11. 10.53 12. 10.85 13. 10.51 14. 10.77 15. 10.82 16. 10.74 17. 11.03 18. 11.10 19. 10.78 20. 11.09 **Other outcome measures (mean):** NR	**Total net benefit at £20k WTP threshold:** 1. £172,338 2. £176,304 3. £182,946 4. **£183,393** 5. £183,254 6. £183,252 7. £183,285 8. £183,103 9. £168,451 10. £174,354 11. £169,869 12. £178,177 13. £166,590 14. £170,141 15. £168,578 16. £165,674 17. £168,604 18. £168,645 19. £160,964 20. £133,701 ICERs: 1. Least effective, least cost

Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value in Health. 2010; 13(8):922-933. Ref ID: DAKIN2010A				
	1. BSC 2. LAM then BSC 3. LAM then TDF 4. TDF then LAM 5. TDF then TDF+LAM 6. TDF then TDF+LAM then ETV 7. TDF then BSC 8. TDF then ETV 9. LAM then ETV 10. LAM then ADV 11. ADV then LAM 12. LAM then TDF+LAM 13. LAM then ADV+LAM 14. ADV then TDF 15. ADV then TDF+LAM 16. ADV then ADV+LAM 17. ETV then LAM 18. ETV then TDF 19. ADV+LAM then TDF+LAM 20. ETV+ADV then LAM	**Cost components incorporated:** drugs, consultations, compensated and decompensated cirrhosis, HCC (including liver transplant),		2. £9,636 vs 1 3. £14,064 vs 2 4. £19,084 vs 3 5. £24,992 vs 5 6. £38,474 vs 6 Interventions 7 to 20 were dominated or extendedly dominated by interventions 1 to 6. CI: NR Probability cost-effective (20k WTP): TDF as first line: 46% LAM then TDF: 25% Probability cost-effectiven (30k WTP): TDF as first line: 78% First-line TDF dominated first-line ETV in 76% of simulations First-line TDF dominated LAM then TDF in 47% of simulations **Other:** NR **Subgroup analyses:** Rerunning the results for specific patient subgroups demonstrated that first-line TDF is most cost-effective for HBeAg positive and HBeAg negative patients and for

Dakin H, Bentley A, Dusheiko G. Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value in Health. 2010; 13(8):922-933. Ref ID: DAKIN2010A				
				patients with and without compensated cirrhosis at willingness to pay over £22,200 per QALY. **Analysis of uncertainty:** Results sensitive to time horizon: when all costs and benefits occurring 19 years in the future were excluded, no treatment was cost-effective compared to LAM then BSC at a £20k WTP threshold.
Data sources				
Health outcomes: transition probabilities from a network meta-analysis{Dakin, 2010 DAKIN2010 /id} **Quality-of-life weights:** Health state utilities for most disease states were based on standard gamble valuations of each health state from a study of UK CHB patients[5]. Quality of life of HBsAg-seroconverted patients was based on UK population norms from Kind et al 1998. Quality of life of patients in the HBeAg-seroconverted state was assumed to be 1% lower than population norms, based on a previous economic evaluation[6]. **Cost sources:** Estimates of resource use and cost for managing severe liver disease were based on a large, retrospective UK microcosting study of patients with chronic hepatitis C. The assumption was made that these costs were unlikely to differ between patients with hepatitis C and hepatitis B. The cost of managing patients in other disease states was based on clinical estimates of frequency of outpatient consultations for each patient group and the tests that would be performed at each consultation. Unclear as to whether these represent the best available estimates.				
Comments				
Source of funding: Gilead Sciences, makers of tenofovir **Limitations:** Study population is appropriate and may be reflective of the case mix seen in clinical practice, but difficult to know if therapies are more, less or equally cost-effective in both HBeAg positive and negative and with and without compensated cirrhosis; unclear how closely effect estimates match the clinical evidence review; estimates of resource use associated with severe liver disease taken from costing study among hepatitis C patients (is this reasonable?); potential conflict of interest.				
Overall applicability*: Minor limitations **Overall quality**:** Partially applicable				

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Orlewska E, Zammit D, Yuan Y et al. The cost-effectiveness analysis of entecavir in the treatment of chronic hepatitis B (CHB) patients in Poland. Experimental and Clinical Hepatology. 2008; 4(3-4):20-28. Ref ID: ORLEWSKA2008				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** Markov model wherein patients may develop viral resistance with continued drug use or viral rebound after treatment cessation; viral load used as predictor of liver disease progression. **Perspective:** health care payer **Time horizon:** 10 years **Treatment effect duration:** 1 year treatment effects used with assumption that 50% will rebound following treatment discontinuation	**Population:** Patients with chronic hepatitis B who were refractory to lamivudine; mixed population of HBeAg positive and negative patients **Cohort settings:** Start age =NR M = NR **Intervention 1:** Entecavir, 1 mg/day, 10 years **Intervention 2:** Adefovir, 10 mg/day, 10 years	**Total costs (mean per patient):** **Men:** Intvn 1: 9,201 Intvn 2: 13,445 Incremental (1-2): -4,243 (CI: NR) **Women:** Intvn 1: 9,327 Intvn 2: 13,617 Incremental (1-2): -4,290 (CI: NR) **Currency & cost year:** 2006 PLN (presented here as 2006 UK pounds‡) **Cost components incorporated:** Direct medical costs, including costs attributable to managing patients with compensated and decompensated cirrhosis and HCC. Costs of treatment related to monitoring and	**Primary outcome measure:** QALYs lost (mean per patient) **Men:** Intvn 1: 0.55 Intvn 2: 0.83 Incremental (1-2): -0.26 (CI: NR) **Women:** Intvn 1: 0.61 Intvn 2: 0.90 Incremental (1-2): -0.29 (CI: NR) **Other outcome measures (mean):** Life years lost **Men:** Intvn 1: 0.59 Intvn 2: 0.86 **Women:** Intvn 1: 0.64 Intvn 2: 0.94	**Primary ICER (Intvn 2 vs Intvn 1):** Entecavir dominates adefovir Probability cost-effective: NR **Other:** Entecavir dominates adefovir in terms of life years gained **Subgroup analyses:** None **Analysis of uncertainty:** Model results were insensitive to variations in health state utilities for compensated and decompensated cirrhosis and HCC, age at initiation of therapy, treatment duration, discounting rate and estimated treatment cost per health state.

Orlewska E, Zammit D, Yuan Y et al. The cost-effectiveness analysis of entecavir in the treatment of chronic hepatitis B (CHB) patients in Poland. Experimental and Clinical Hepatology. 2008; 4(3-4):20-28. Ref ID: ORLEWSKA2008				
Discounting: Costs = 5%; Outcomes = 5%		adverse events were excluded on the assumption that they were the same for all treatments.		

Data sources

Health outcomes: Treatment effects were based on an indirect comparison of serum HBV DNA levels observed in randomised clinical trials. For Entecavir, the data came from Sherman et al[7] and for adefovir, the data came from Peters et al[8]. In the absence of data regarding rebound rates following discontinuation of treatment, 50% was assumed across all drugs. No resistance was assumed to develop for either entecavir or adefovir.

Incidence of liver complications was taken from the REVEAL-HBV study: incidence rates, average time to an event (compensated and/or decompensated cirrhosis and HCC). Life expectancy for CHB patients was estimated using age- and gender-specific data for the Polish population. Life expectancy for CHB and compensated cirrhosis health states were assumed to be the same as for the normal non-diseased population. For HCC and decompensated cirrhosis, life expectancy was estimated using the DEALE method.

Quality-of-life weights: Due to a lack of data specific to the Polish population, published estimates from a British population were used. Note that the utility reported for the compensated cirrhosis population is 0.01 higher than for the CHB population.

Cost sources: Unit costs of drugs were based on gross wholesale price (no reference provided) and resource use was based on the adherence rates observed in the clinical trials. Resource use and cost estimates for compensated and decompensated cirrhosis and HCC were derived from retrospective analyses of patient medical records and expert opinion.

Comments

Source of funding: Bristol-Myers Squibb International, manufacturers of entecavir

Limitations: : The study includes two comparators of interest, but not all comparators relevant to the review question (e.g. tenofovir is missing); costing perspective is health care payer in Poland, thus some uncertainty about applicability of Polish unit costs and estimates of resource use; costs and effects discounted at 5% per annum (3.5% preferred by NICE); changes in health-related quality of life estimated by general UK population, but estimates differ from other published CEAs that reference the same/similar study; no differentiation between HBeAg positive and negative CHB patients; unclear how closely treatment effect estimates match the NCGC clinical review; unclear whether estimates of cost and resource use are from best available sources; potential conflict of interest (funded by Bristol Meyers Squibb, makers of entecavir)

Other: None.

Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

Abbreviations: CI = confidence interval; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs =quality-adjusted life years
‡ Converted using 2006 purchasing power parities{Organisation for Economic Co-operation and Development (OECD), 2011 OECD2011 /id}

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Jones J, Shepherd J, Baxter L et al. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. Health Technology Assessments. 2009; 13(35):1-172. Ref ID: JONES2009				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision model **Approach to analysis:** Eight-state Markov model used to extrapolate long-term outcomes and life time costs based on short-term outcomes including HBeAg seroconversion (for HBeAg positive patients) and ALT normalisation (for HBeAg negative patients) **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration:**	**Population:** Mixed population: 70% HBeAg positive and 30% HBeAg negative **Cohort settings:** Start age = 32 years (HBeAg positive); 40 years (HBeAg negative) M = 70% (HBeAg positive); 90% (HBeAg negative) **Intervention 1:** Best supportive care **Intervention 2:** Interferon-α 2a **Intervention 3:** Interferon-α 2a then lamivudine **Intervention 4:** Interferon-α 2a then adefovir **Intervention 5:** Interferon-α 2a then LAM then adefovir **Intervention 6:**	**Total costs (mean and 95% CI per patient):** Intvn 1: £11,007 (9079 to 13,355) Intvn 2: £15,024 (13164 to 17289) Intvn 3: £17,811 (15881 to 20184) Intvn 4: £32,713 (28737 to 37153) Intvn 5: £33,946 (29470 to 39012) Intvn 6: £18,128 (16265 to 20309) Intvn 7: £20,744 (18745 to 23119) Intvn 8: £33,966 (29667 to 38788) Intvn 9: £34,810 (30,068 to 40,213) **Currency & cost year:** 2006/07 UK pounds **Cost components incorporated:** Direct health care costs including laboratory and diagnostic tests, outpatient visits, differential monitoring costs for treated and untreated patients, HCC screening, drugs, management of progressive liver disease and liver transplantation	**Primary outcome measure:** QALYs (mean and 95% CI per patient) Intvn 1: 11.99 (11.07 to 12.77) Intvn 2: 12.38 (11.46 to 13.16) Intvn 3: 12.80 (11.86 to 13.61) Intvn 4: 13.32 (12.40 to 14.11) Intvn 5: 13.40 (12.47 to 14.20) Intvn 6: 12.65 (11.74 to 13.45) Intvn 7: 13.03 (12.09 to 13.86) Intvn 8: 13.48 (12.56 to 14.29) Intvn 9: 13.55 (12.62 to 14.33) **Other outcome measures (deterministic mean):** Discounted life years Intvn 1: 16.42 Intvn 2: 16.86 Intvn 3: 17.35 Intvn 4: 17.97 Intvn 5: 18.08 Intvn 6: 17.18 Intvn 7: 17.62 Intvn 8: 18.16 Intvn 9: 18.25	**Incremental analysis ICERs (pa):** Intvn 3: £8,400 vs Intvn 1 Intvn 7: £12,752 vs Intvn 3 Intvn 9: £27,050 vs Intvn 7 Probability cost-effective at 20k threshold: Intvn 7 (75%) Probability cost-effective at 30k threshold: intvn 9 (68%) **Subgroup analyses:** NR **Analysis of uncertainty:** A series of deterministic sensitivity analyses were performed around variables including: • Transition probability from compensated cirrhosis to HBeAg seroconversion • Transition probability from HBsAg seroconversion to HCC • Transition probability to HBsAg seroconversion • Discounting rates (6% for costs; 1.5% for benefits) • Proportion male in HBeAg positive

Jones J, Shepherd J, Baxter L et al. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. Health Technology Assessments. 2009; 13(35):1-172. Ref ID: JONES2009				
Discounting: Costs = 3.5%; Outcomes = 3.5%	Pegylated Interferon-α 2a **Intervention 7:** Pegylated Interferon-α 2a then lamivudine **Intervention 8:** Pegylated Interferon-α 2a then adefovir **Intervention 9:** Pegylated Interferon-α 2a then lamivudine then adefovir			cohort • Proportion male in HBeAg negative cohort • Proportion HBeAg positive in baseline cohort • Starting age for cohort • Rates of ADV resistance • Utility gain from seroconversion • Age-specific utilities • Cost of compensated cirrhosis state • PEG-α cost • ADV cost Only 5 deterministic SAs had any effect on the results|: • If patients with compensated cirrhosis cannot achieve HBeAg seroconversion, ICER for treatments containing ADV salvage increase (i.e. become less favourable) • If proportion of baseline cohort that is HBeAg positive is lower, ICER for treatments containing ADV salvage increase (i.e. become less favourable) • If starting age of cohort increases, ICERs for all strategies increase (i.e. become less favourable). QALY gains decrease by 15-20%, whereas incremental costs are reduced by 2-

Jones J, Shepherd J, Baxter L et al. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. Health Technology Assessments. 2009; 13(35):1-172. Ref ID: JONES2009				
				6%. • If utility gain from seroconversion is reduced, ICERs for all strategies increase (i.e. become less favourable) • Alternative discounting rates (1.5% for benefits and 6% for costs) produces more favourable ICERs

Data sources

Health outcomes: Estimates of effect were derived from a systematic review of the clinical effectiveness of pegylated interferon-α 2a and adefovir. Natural history parameters were used to represent estimates of baseline risk for the strategy of best supportive care (i.e. no treatment). These parameters were derived from a variety of sources, including previous systematic reviews and meta-analyses (Shepherd 2004; Wong 1993), economic analyses[6,9,10] (Bennett 1997), natural history studies[11](Liaw 1998) (Fattovich 1991; Fattovich 2003) and clinical consensus (de Franchis 2003; di Bisceglie 1988; Lavanchy 2004).

HBeAg positive CHB: One-year HBeAg seroconversion rates were taken from RCTs. Estimates for PEG-2a (32%) was taken from Lau 2004; estimates for INF-2a (25%), from Cooksley 2003[12]; estimates for LAM(18%) and ADV (18%), from Marcellin 2003[13] and Lau 2004. Longer-term seroconversion rates for LAM and ADV were taken from Lok 2004, Leung 2001[14] and Liaw 2000[15]. Durability of HBeAg seroconversion was estimated using Kaplan-Meier estimates of cumulative relapse rates for treated patients from van Nunen 2003: 9% for INF-2a and PEG-2a, 25% for LAM and 9% for ADV. These estimates were applied to patients who underwent seroconversion while on treatment and only for the year immediately following seroconversion, after which relapse risk reverts to the spontaneous reactivation rate. In the absence of data for the durability of seroconversion following treatment with PEG-2a, it was assumed to be the same as for INF. For non-seroconverted patients receiving LAM, the transition rate from CHB to compensated cirrhosis was reduced for the first year of treatment, based on a pooled analysis of three RCTs (Goodman 1999).

HBeAg negative CHB: Proportions of patients normalising ALT were taken from RCTs[16,17] for PEG-2a (59%), LAM (73%) and ADV (72%). Review articles (Hadziyannis 2001; Lavanchy 2004; Papatheodoridis 2004) have reported biochemical response rates for INF-2a of 50%. Durability of response was estimated using with long-term follow-up of LAM-treated patients (Santantonio 2000; Santantonio 2002[18]; Tassopoulos 1991) an 80% reactivation rate is applied in the year in which resistance develops and effective treatment ceases. In the absence of long-term follow-up data on ADV in this group of patients, the same assumptions as for LAM were applied. For PEG-2a, reactivation of CHB in the year following treatment is assumed to occur in 25% of patients who showed an initial response to treatment. For INF-2a, reactivation in the year following treatment is assumed to occur in 60-70%.

Quality-of-life weights: Age- and sex-adjusted utility values elicited from 100 HBV infected patients and 100 uninfected respondents in the UK [5] were used in the base case. Utility values used in the 2006 report[4] were used in a sensitivity analysis. For this, the authors assumed that patients who experienced HBsAg or HBeAg seroconversion had the same level of HRQoL as healthy individuals (using published age-specific QoL weights for a healthy population). Utility values for other states were estimated relative to those values using the same assumptions as Wong and colleagues[6], where the weight for CHB is 0.04 less than the equivalent age-specific value for a

Jones J, Shepherd J, Baxter L et al. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. Health Technology Assessments. 2009; 13(35):1-172. Ref ID: JONES2009
healthy individual. Health state utilities for progressive liver disease (compensated and decompensated cirrhosis, HCC, liver transplant and post-liver transplant) were taken from EQ-5D estimates for a population with chronic hepatitis C (Wright 2005; Ratcliffe 2002). **Cost sources:** Estimates of additional resource use required for monitoring patients while on treatment were identified based on clinical guidelines and discussions with hepatolotists/specialist nurses at Southampton General Hospital Trust. The same sources were used to estimate the resource use for routine monitoring of untreated patients in the seroconverted and CHB health states. Health state costs for compensated cirrhosis, decompensated cirrhosis and HCC were taken from an observational study conducted during an HTA funded trial in mild hepatitis C (Wright 2005). Costs for liver transplantation and post-liver transplantation were taken from a Department of Health-funded study of the cost of liver transplantation (Longworth 2001). These costs were all derived for the 2006 report[4] and were inflated to 2006-07 prices using the Hospital and Community Health Services Pay and Prices Index. Unit costs for drugs were taken from the *British National Formulary* (March 2008).
Comments
Source of funding: The research was commissioned and funded by the National Institute for Health Research Health Technology Assessment programme; **Limitations:** The study includes three comparators of interest, but not all comparators relevant to the review question (e.g. tenofovir, entecavir and combinations are missing as are strategies starting with any treatment other than interferon or pegylated interferon); normalisation of ALT used as key indicator of response for HBeAg negative patients (is this a limitation?); unclear how closely treatment effect estimates match the NCGC clinical review **Other:**
Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

F.1.4 Decompensation and advanced cirrhosis

F. Kanwal, M. Farid, P. Martin, G. Chen, I.M. Gralnek, G.S. Dulai, B.M.R. Spiegel. Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis. American Journal of Gastroenterology. 2006. 101; 2076-2089. Ref ID: KANWAL2006

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** A Markov model was developed to compare lamivudine to adefovir and entecavir alone and as 'salvage' therapies after the development of resistance to lamivudine. Patients enter the model with either compensated or decompensated cirrhosis. At each one year cycle people can progress to decompensated cirrhosis, back to compensated cirrhosis, and back to decompensated again. Hepatocellular carcinoma could	**Population:** People with chronic hepatitis B cirrhosis and active viral replication. It was assumed that 50% of the population had compensated cirrhosis and 50% decompensated cirrhosis. **Cohort settings:** Start age = 50 years old M = NR **Intervention 1:** No HBV treatment **Intervention 2:** Lamivudine monotherapy (100mg once daily for an indefinite period) **Intervention 3:** Adefovir monotherapy (10mg once daily for an indefinite period). People developing resistance continued receiving long term adefovir. Transplanted patients	**Total costs (mean per patient):** Intvn 1: £71,835 Intvn 2: £91,717 Intvn 3: £86,948 Intvn 4: £112,241 Intvn 5: £90,235 Intvn 6: £118,014 (rough estimate based on graph) **Currency & cost year:** 2005 US dollars (presented here as 2005 UK pounds‡) **Cost components incorporated:** Drug costs (per month): Lamivudine = £100 Adefovir = £378 Entecavir = £458 5ml injection of HBIG = £435 Non drug costs: Per physician visit = £33 Set laboratory tests = £51	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: 3.3 Intvn 2: 4.2 Intvn 3: 4.5 Intvn 4: 4.6 Intvn 5: 4.7 Intvn 6: 4.4 (rough estimate based on graph) **Other outcome measures (mean):** None	**Primary ICER:** Intvn 3 vs Intvn 1 = £12,595 per QALY gained Intvn 5 vs Intvn 3 = £16,436 per QALY gained **Probability cost-effective:** At a threshold of £20k, there was approximately a 55% probability that entecavir monotherapy (Intvn 5) is cost effective compared to adefovir monotherapy (Intvn 3). **Other:** None **Subgroup analyses:** Although the methods section said the proportion of the population beginning the model with compensated and decompensated cirrhosis was varied in SA, the results of this analysis were not reported. **Analysis of uncertainty:** One way sensitivity analysis showed that the model was most sensitive to the cost of adefovir and entecavir, and annual rate of progression from compensated to decompensated cirrhosis with each drug.

F. Kanwal, M. Farid, P. Martin, G. Chen, I.M. Gralnek, G.S. Dulai, B.M.R. Spiegel. Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis. American Journal of Gastroenterology. 2006. 101; 2076-2089. Ref ID: KANWAL2006				
develop at any stage. People with decompensated cirrhosis or heparocellular carcinoma were eligible for liver transplant. Following transplant, people could, develop recurrent Hep B cirrhosis. **Perspective:** USA, Third party healthcare payer **Time horizon:** Lifetime **Discounting:** Costs = 3%; Outcomes = 3%	received prophylaxis with a combination of monthly HBIG and daily adefovir. **Intervention 4:** Lamivudine (100mg once daily) with crossover to adefovir (10mg once daily) on resistance ('adefovir salvage'). People who did not develop resistance remained on lamivudine. Therefore, adefovir was only reserved for patients who develop viral resistance on lamivudine. **Intervention 5:** Entecavir monotherapy (0.5mg once daily for an indefinite period). Patients developing viral resistance continued receiving long term entecavir. **Intervention 6:** Lamivudine (100mg once daily) with crossover to entecavir (0.5mg once daily) on resistance ('entecavir salvage'). People who did not develop viral resistance remained on lamivudine.	Abdominal ultrasound = £95 Cirrhosis care costs: Per year compensated = £613 First year following variceal haemorrhage = £14,274 Per subsequent year following variceal haemorrhage = £2,794 Per year ascites = £2,581 First year encephalopathy = £9.162 Per subsequent year following encephalopathy = £2,122 Liver transplant = £81,089 Per year follow-up care post liver transplant = £14,161 Hepatocellular carcinoma = £24,623		

F. Kanwal, M. Farid, P. Martin, G. Chen, I.M. Gralnek, G.S. Dulai, B.M.R. Spiegel. Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis. American Journal of Gastroenterology. 2006. 101; 2076-2089. Ref ID: KANWAL2006				
	Therefore, entecavir was reserved for patients developing resistance on lamivudine.			
Data sources				
Health outcomes: The authors conducted a systematic review to identify studies of the natural history of cirrhosis, including the post-transplantation course, or the efficacy of lamivudine, adefovir, or entecavir in the treatment of pre- and post-transplantation HBV. **Quality-of-life weights:** Utilities for cirrhosis that were elicited using standard gamble in patients with hepatitis C were assumed to apply to the same health state in this model (0.82 for compensated cirrhosis, 0.60 for decompensated, 0.86 following successful liver transplant, 0.73 for hepatocellular carcinoma; all from Chong 2003). **Cost sources:** Costs for physician services and procedures were obtained from the 2005 Medicare Fee Schedule; pharmaceutical costs were average wholesale prices listed in the 2006 Red Book; costs for cirrhosis and related health states were obtained from a published study of inpatient and outpatient costs (Bennett 1997).				
Comments				
Source of funding: F.K. is supported by a Veteran's Administration Health Services Research and Development Ambulatory Care Fellowship Award and American Association for the Study of Liver Disease Advanced Hepatology Fellowship Award; B.S. is supported by a VA HSR&D Career Development Award and American Gastroenterological Association Outcome Research Award; The author's department at UCLA/VA Centre for Outcomes Research and Education is supported by the CURE Digestive Diseases Research Centre Grant (NIH; This research was also supported by an investigator-initiated research award by Gilead Sciences, Inc. **Limitations:** quality of life estimates were adapted from people with Hepatitis C, not HBV; triangular distribution assumed for all inputs; results of probabilistic analysis not fully reported. Baseline population was 50% compensated cirrhosis and 50% decompensated cirrhosis – results were not reported separately and results of sensitivity analysis varying these proportions was not reported; comparative effectiveness of entecavir based on histological improvement with no long term resistance data (1% per year was assumed).				
Overall applicability*: Partially applicable **Overall quality**: Minor limitations**				

Abbreviations: CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; QALYs =quality-adjusted life years
‡ Converted using 2005 purchasing power parities{Organisation for Economic Co-operation and Development (OECD), 2011 OECD2011 /id}

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitation*

F.1.5 Pregnant women

H. Hung and H. Chen. Cost-effectiveness analysis of prophylactic lamivudine use in preventing vertical transmission of hepatitis B virus infection. Pharmacoeconomics. 2011. 29(12):1063 – 1073. Ref ID: HUNG2011				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** A systematic literature search was preformed to identify studies comparing lamivudine to control therapy for prophylactic HBV treatment. The natural history model was built with a focus on high endemic areas in Asia. The model was run probabilistically **Perspective:** Taiwanese societal perspective **Time horizon:** Lifetime **Treatment effect duration:** NR	**Population:** Pregnant carriers of HBV and their children **Cohort settings:** Start age = Newborns M = NR **Intervention 1:** **Routine care** No prophylactic treatment for mother. (Vaccine and HBIG given to neonate). **Intervention 2:** **Prophylactic lamivudine** Lamivudine given orally to mother in third trimester. (Vaccine and HBIG given to neonate).	**Total costs (mean per patient):** Intvn 1: £12,443 Intvn 2: £12,420 Incremental (2-1): -£23 (CI NR; p = NR) **Currency & cost year:** 2008 US dollars (presented here as 2008 UK pounds‡) **Cost components incorporated:** HBsAg test = £4 HBsAg test = £6 Vaccine per birth = £6 HBIG per birth = £48 LAM per woman = £152 Symptomatic acute infection = £1, 525 Asymptomatic acute infection = £0 Fulminant hepatitis = £17,807 Asymptomatic carrier = £171 Chronic active hepatitis = £2,379 Compensated cirrhosis = £21,418 Decompensated cirrhosis = £28,689 HCC = £36,540 Taiwan's per capita income = £11,218	**QALYs** **(mean per patient):** Intvn 1: 69.8923 Intvn 2: 69.8947 Incremental (2-1): 0.0024 (CI NR; p = NR) **Other outcomes:** **Infections** **(mean per patient):** Intvn 1: 0.540 Intvn 2: 0.310 Incremental: 0.23	**ICER (Intvn 2 vs Intvn 1):** Lamivudine prophylaxis was more effective (0.0024 QALYs gained) and £23 less costly than routine treatment. At a threshold of $20,000 (£12,790), there was a 94% probability that lamivudine was cost effective. **Analysis of uncertainty:** A sensitivity analysis was done in which productivity loss was excluded from the model. The authors report that under this scenario lamivudine was still dominant, however QALYs were not reported.

Discounting: Costs = 3% ; Outcomes = NR				

Data sources

Health outcomes: The authors conducted a meta-analysis of three studies (Li 2003{Li, 2003 LI2003 /id}, van Zonneveld 2003{van Zonneveld, 2003 9 /id}, Xu 2009{Xu, 2009 XU2009 /id}) to identify the risk of transmission on lamivudine therapy compared to control. They found that lamivudine halved perinatal transmission with a RR of 0.52 (95% CI 0.24, 0.94). Vaccine coverage in Taiwan ranges from 87% to 94% (Chen 1996, Lin 1988); the efficacy of vaccination with HBIG injection was reported as 97% from a 15-year follow-up (Beasley 1983); the prevalence of HBV carrier in pregnant women and HBeAg positive status in HBV carrier mothers was 9.5% and 41% respectively in highly endemic Asian areas (Edmunds 1996); in one-third of women, serum HBV DNA exceeded 150pg/mL in a Dutch study (del Canho 1997); the probability of vertical transmission reported to be 13% to 89% depending on viral status of the mothers (del Canho 1997; Edmunds 1996; Ip 1989; Lee 1986); the probability of becoming a carrier varies with age of acquiring infection (Edmunds 1993), as does the probability of having fulminant hepatitis after acute infection and the mortality after fulminant hepatitis (Tassopoulos 1987; Dupuy 1975; Redeker 1975; Karvountzis 1974). **Quality-of-life weights:** Utility values were obtained from a previous cost-effectivness study on prevention of hepatitis B in Asian and Pacific Islander adults (Hutton 2007). **Cost sources:** Vaccine and healthcare costs were determined from minimum, mode, and maximum estimates in the literature and assigned a triangular distribution. Indirect costs were estimated by production loss due to early death (estimated using Tiwan's per capita income multiplied by the offset between the age of death and age of retirement (65 years)).

Comments

Source of funding: NR **Limitations:** The authors of this study claim to have conducted it from a Taiwanese societal perspective. As per protocol, this study would normally be excluded from the economic evidence review. However, the costs used to inform this model were obtained from American, Israeli and Italian publications. Therefore, from a costing perspective this study is more applicable than it first appears. Although the model transition probabilities were taken from studies with 'an emphasis on high endemic areas in Asia', the figures quoted appear applicable to a UK perspective. A major limitation of the analysis was that it included the cost of lost productivity due to early death. This was calculated using Taiwan's per capita income multiplied by the number of years between the age of death and average age of retirement (65 years). Although these costs have been excluded in sensitivity analysis, the authors have not reported the results of this analysis numerically. **Other:** QALYs do not appear to have been discounted.

Overall applicability*: Partially applicable Overall quality: Potentially serious limitations**

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = 95% confidence interval; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years

*‡ Converted using 2008 purchasing power parities{Organisation for Economic Co-operation and Development (OECD), 2011 OECD2011 /id} * Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

F.2 Surveillance

C. J. Thompson, G. Rogers, P. Hewson, D. Wright, R. Anderson, M. Cramp, S. Jackson, S. Ryder, A. Price, and K. Stein. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. Health Technol. Assess. 11 (34):1-206, 2007. Ref ID: THOMPSON2007A				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** A systematic literature search was performed to identify studies comparing different screening methods and frequencies. The model was based on a general population of patients with compensated cirrhosis but a subgroup analysis was carried out on patients with hepatitis B virus. Results reported here will focus on the hep B group **Perspective:** UK	**Population:** Patients with hepatitis B-induced cirrhosis under the age of 70. **Cohort settings:** Start age = 44 M = 86.5% **Intervention 1:** No surveillance **Intervention 2:** Annual surveillance using AFP triage (Alpha-fetoprotein test as a triage test leading to more sensitive tests.) **Intervention 3:** Annual surveillance using ultrasound alone **Intervention 4:** Annual surveillance using AFP	**Total costs (mean per patient):** Intvn 1: £29,600 Intvn 2: £31,700 Intvn 3: £32,100 Intvn 4: £32,700 Intvn 5: £33,000 Intvn 6: £33,600 Intvn 7: £34,200 Incremental vs previous:: Intvn 2 vs 1: £2,100 Intvn 3 vs 2: £2,500 Intvn 4 vs 3: £3,100 Intvn 5 vs 4: £3,400 Intvn 6 vs 5: £4,000 Intvn 7 vs 6: £4,700 **Currency & cost year:** 2004 UK pounds **Cost components incorporated:** AFP test = £4 Liver ultrasound scan = £50 CT abdomen = £111	**QALYs (mean per patient):** Intvn 1: 10.858 Intvn 2: 11.069 Intvn 3: 11.066 Intvn 4: 11.119 Intvn 5: 11.168 Intvn 6: 11.164 Intvn 7: 11.216 Incremental vs previous: Intvn 2 vs 1: 0.211 Intvn 3 vs 2: 0.208 Intvn 4 vs 3: 0.261 Intvn 5 vs 4: 0.310 Intvn 6 vs 5: 0.306 Intvn 7 vs 6: 0.358	**ICER** Intvn 1: Intvn 2 vs Intvn 1: £10,200 per QALY Intvn 3: Dominated Intvn 4: Extended dominated Intvn 5 vs Intvn 2: £12,700 per QALY Intvn 6: Dominated Intvn 7 vs Intvn 5: £26,800 per QALY **Analysis of uncertainty:** The cost effectiveness acceptability curve shows that 6 monthly surveillance with US and AFP is only cost effective in 10% of the simulations when using a £20,000 per QALY threshold. The AFP triage strategy at 6 months is the cost effective strategy at £20,000 per QALY threshold.

national health service perspective **Time horizon:** Lifetime **Treatment effect duration:** NR **Discounting:** Costs = 3.5% ; Outcomes = 3.5%	and ultrasound **Intervention 5:** 6-monthly surveillance using AFP triage **Intervention 6:** 6-monthly surveillance using ultrasound alone **Intervention 7:** 6-monthly surveillance using AFP and ultrasound	MRI liver = £200 Liver transplant = £21,800 Liver resection = £5,400 Liver transplant (outpatient appointment) = £101 Compensated Cirrhosis = £1,171 Decompensated Cirrhosis = £9,385 Waiting list cost = £1,567 Transarterial chemoembolisation = £537 Percutaneous ethanol injection = £381 Radiofrequency thermal ablation = £754 Best supportive care with untreatable HCC = £1,230 Surgically untreatable HCC_s and HCC_m = £1,619 Surgically untreatable HCC_L= £177		

Data sources

Health outcomes: The authors conducted a systematic review that found no includable studies. The researchers therefore used a mixture of found sources, patient level data and assumptions to inform the parameters of the effectiveness of each of the surveillance mechanisms The studies used to inform the incidence was Fattovich 2004. The tumor growth rate was determined using a study by Taouli et al., 2005. For ultrasound test performance the Bennett 2002 study was used. The accuracy of AFP was determined using individual patient level data from studies by: Sheu et al., 1985, Ebara et al., 1986, Cottone et al., 1988, Oka et al., 1990, Cottone et al., 1994, Zoli et al., 1996 and Trevisani et al., 2001. Fattovich 1997 and 2002 was used to inform the mortality estimates. **Quality-of-life weights:** Utility values were obtained from a study by Chong et al., 2003 of Canadian HCV patients with compensated cirrhosis, decompensated cirrhosis and HCC using four methods of utility estimation (visual analogue scales, standard gamble (SG), HUI version 3 and EQ-5D). **Cost sources**: Costs were obtained primarily from the UK NHS national reference costs 2003/2004. However palliative care costs were taken from hospital cost data from London, Southampton and Newcastle and trial data by Wright et al., 2006.

Comments

Source of funding: UK NHS Health Technology Assessment **Limitations:** The study is limited by the data available, the main inputs for the model were not meta analysed due to the fact that there were no studies to meta analyse. The study did not look at surveillance more frequent than 6 months, such as 3 months in cirrhotic patients which limits the paper ability to answer the question; it also did not look at patients who are non-cirrhotic. The analysis is diluted by the fact that HBV was only a subgroup in the analysis and that some of the more advanced statistics were only done on the population as a whole and not on the HBV population specifically.

Overall applicability*: Partially applicable Overall quality: Minor limitations**

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = 95% confidence interval; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years

** Directly applicable / Partially applicable / Not applicable; ** Minor limitations /Potentially serious limitations / Very serious limitations*

Appendix G: Forest plots

G.1 Diagnosis of liver disease in secondary specialist care

G.1.1 Adults with CHB

Figure 1: AUC (95%CI) plot for fibrosis and cirrhosis – Fibrotest

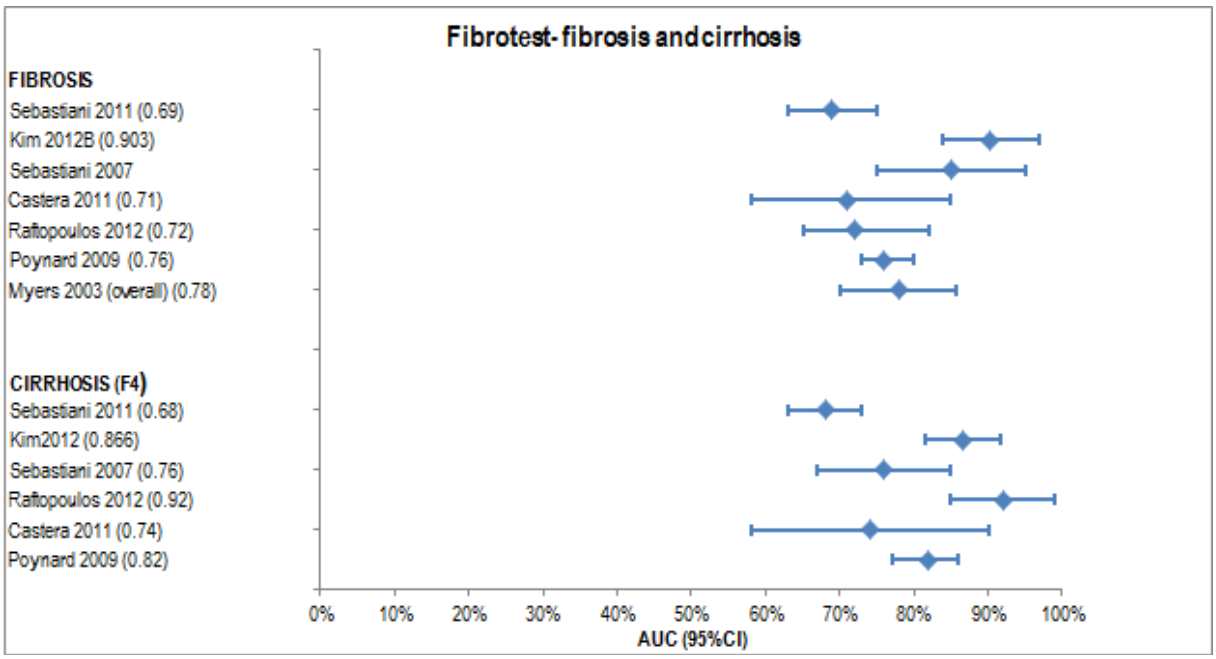


Figure 2: AUC (95%CI) plot for necroinflammatory activity – ActiTest

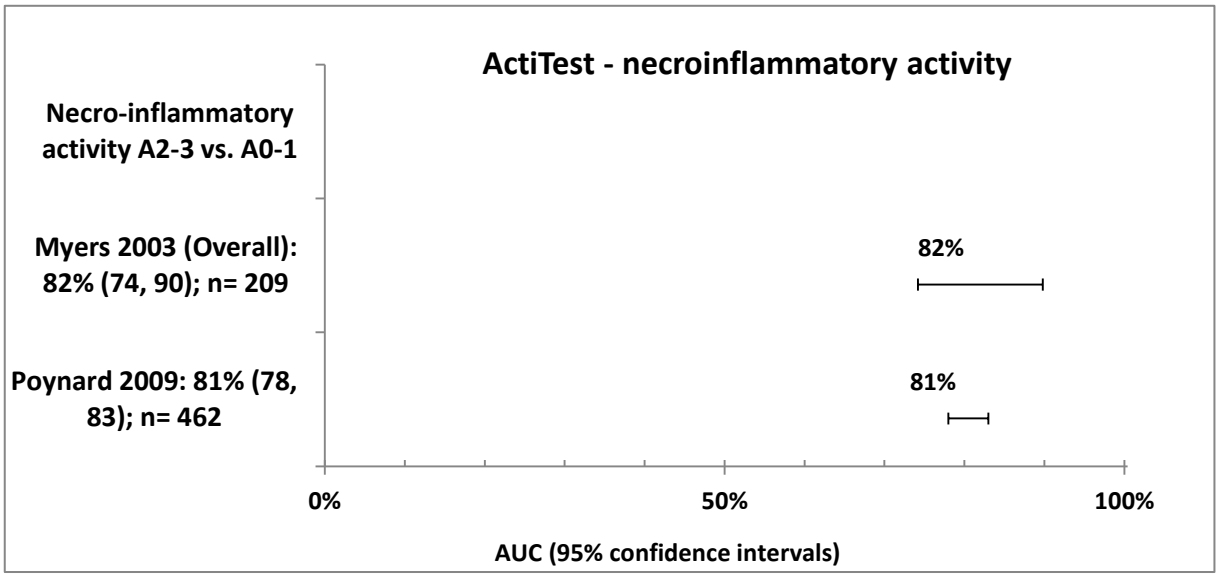
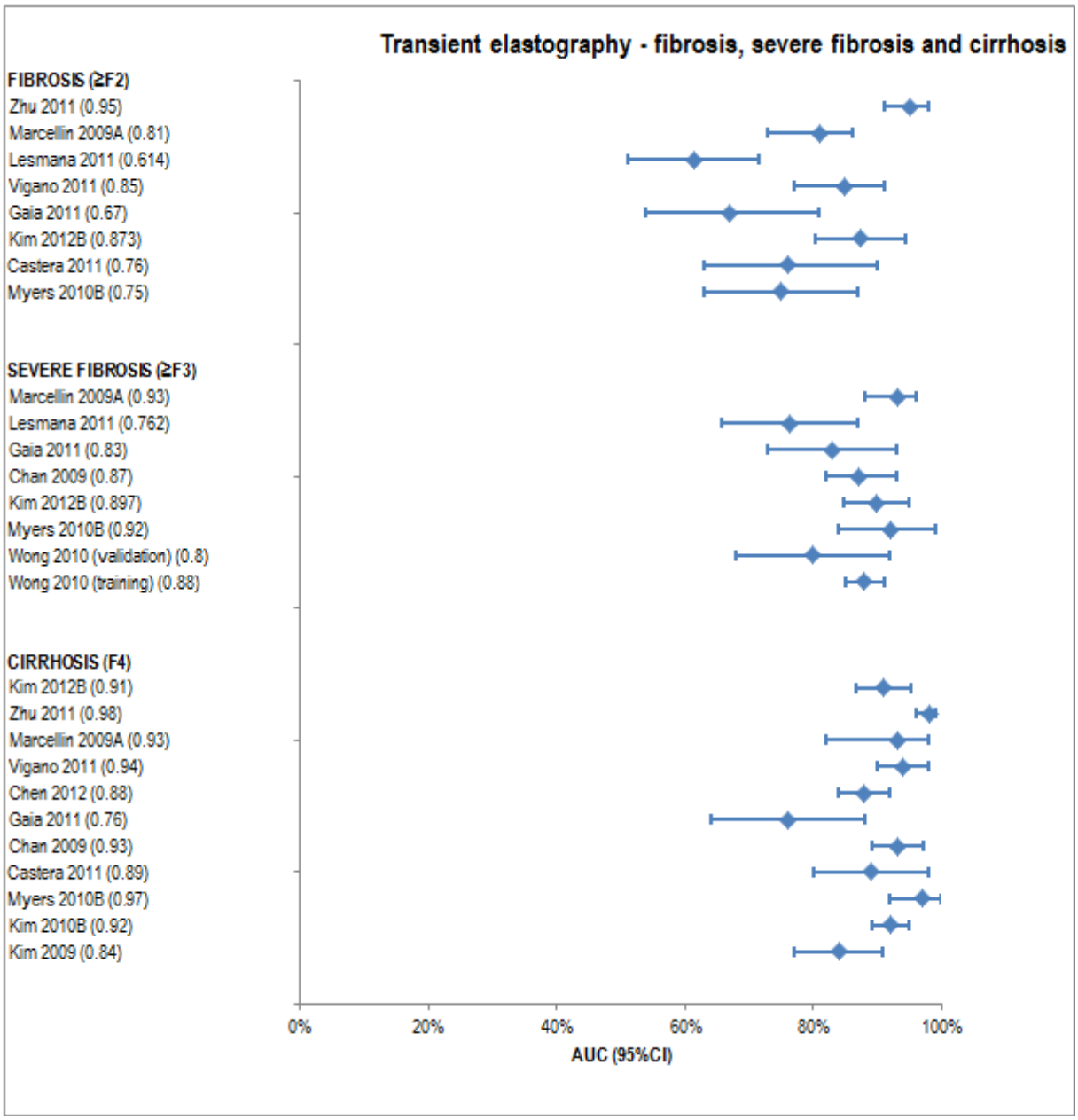
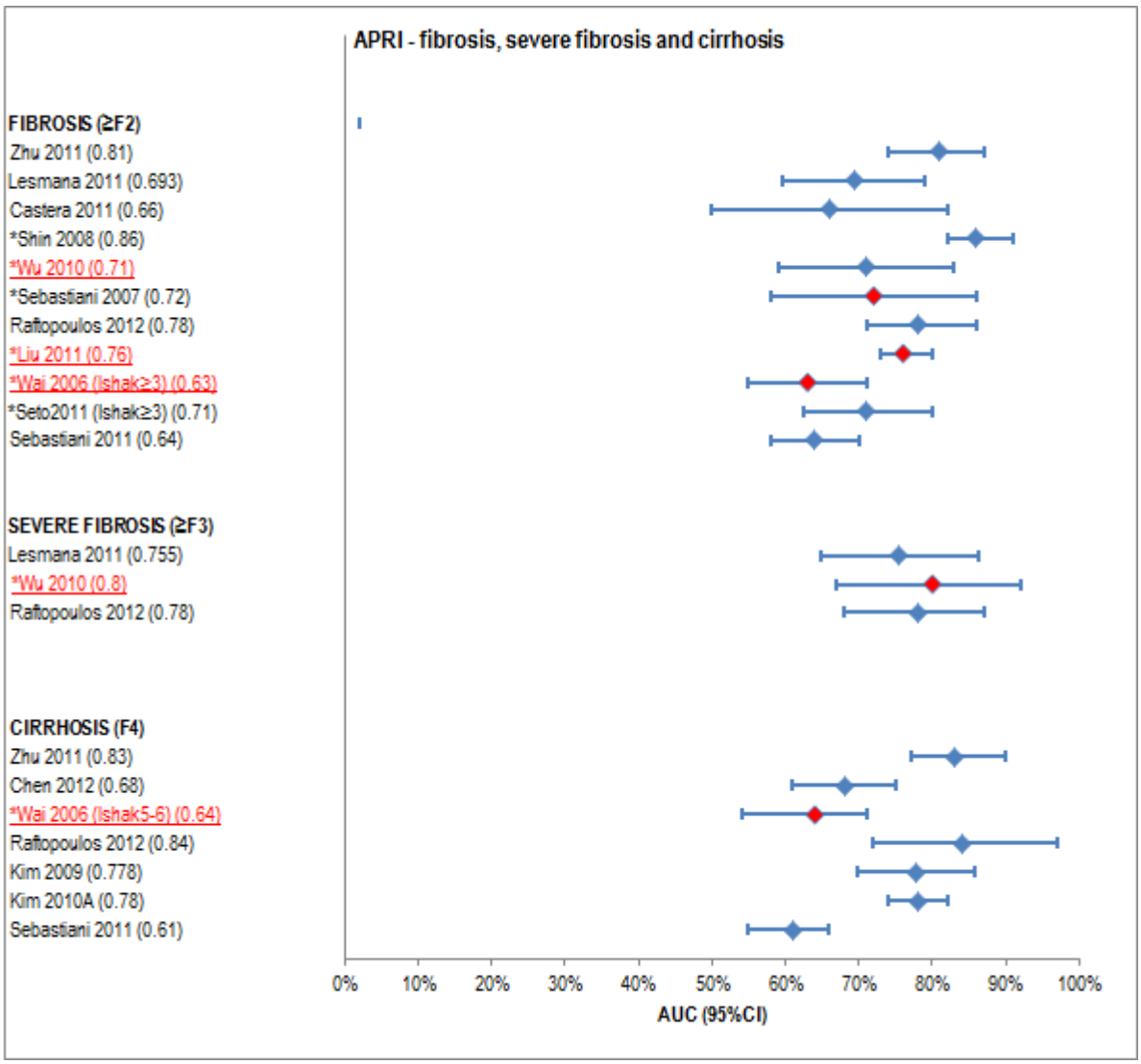


Figure 3: AUC (95%CI) plot * for fibrosis, severe fibrosis and cirrhosis – Transient elastography (FibroScan)



**All studies had a cross-sectional design.*

Figure 4: AUC (95%CI) plot for fibrosis, severe fibrosis and cirrhosis – APRI



**retrospective design; red and underline – studies considered to be at very high risk of bias*

Figure 5: AUC (95%CI) plot for fibrosis, severe fibrosis and cirrhosis – Transient elastography and APRI

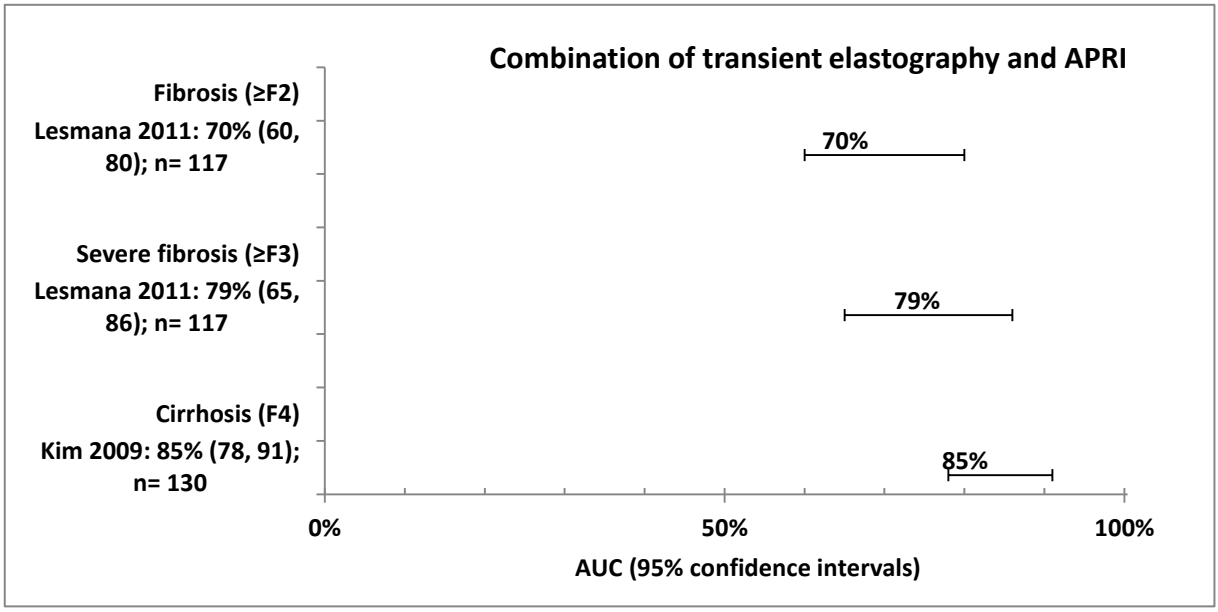


Figure 6: Summary forest plot for fibrosis (≥F2) – sensitivity and specificity at "standard" thresholds

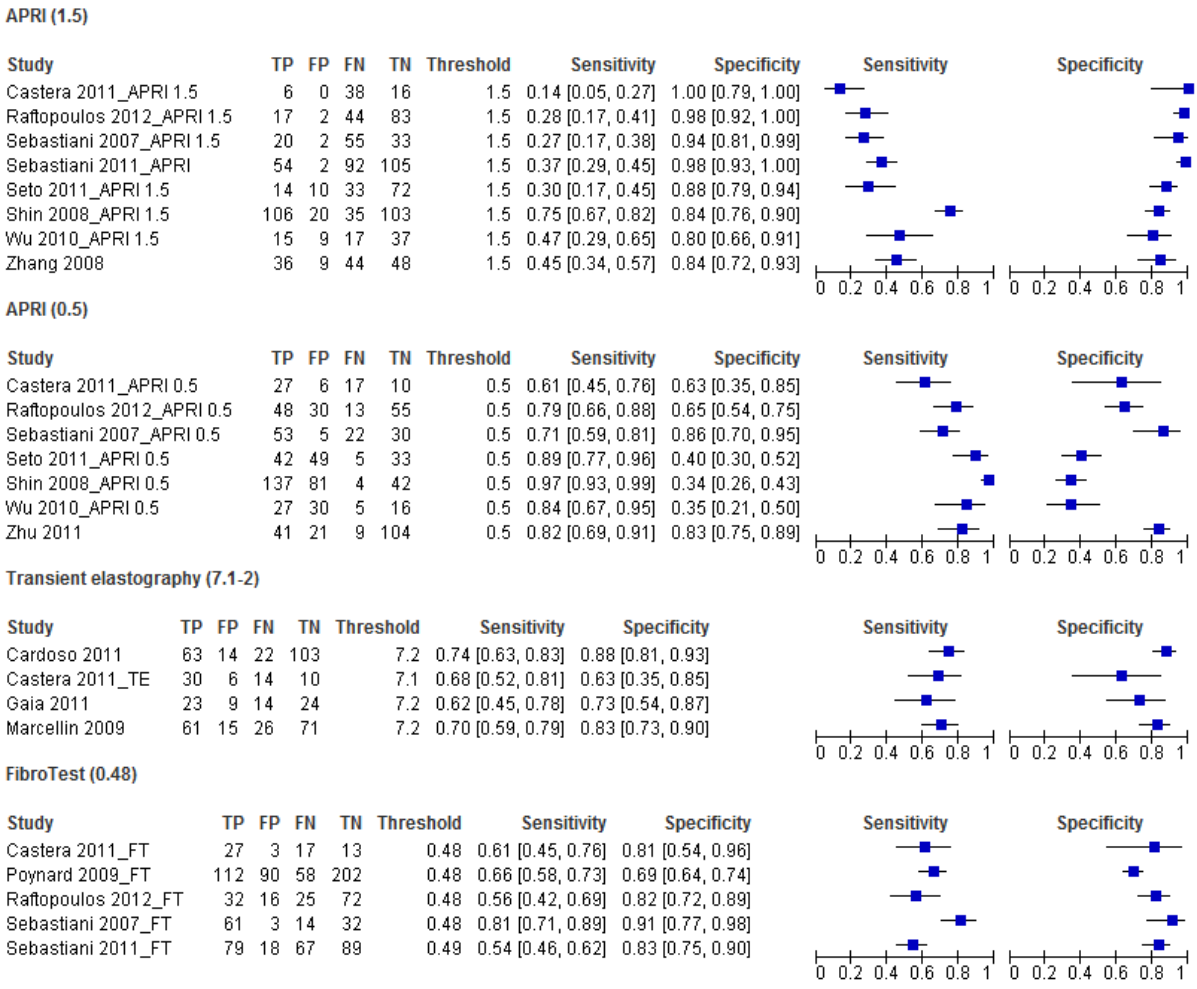


Figure 7: Summary forest plot for necro-inflammatory activity – sensitivity and specificity

ActiTest

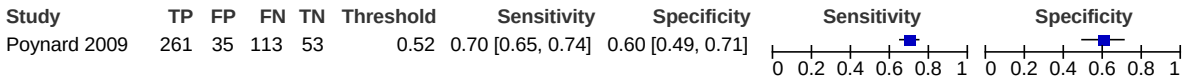


Figure 8: ROC curves for fibrosis (with APRI = 1.5), by test

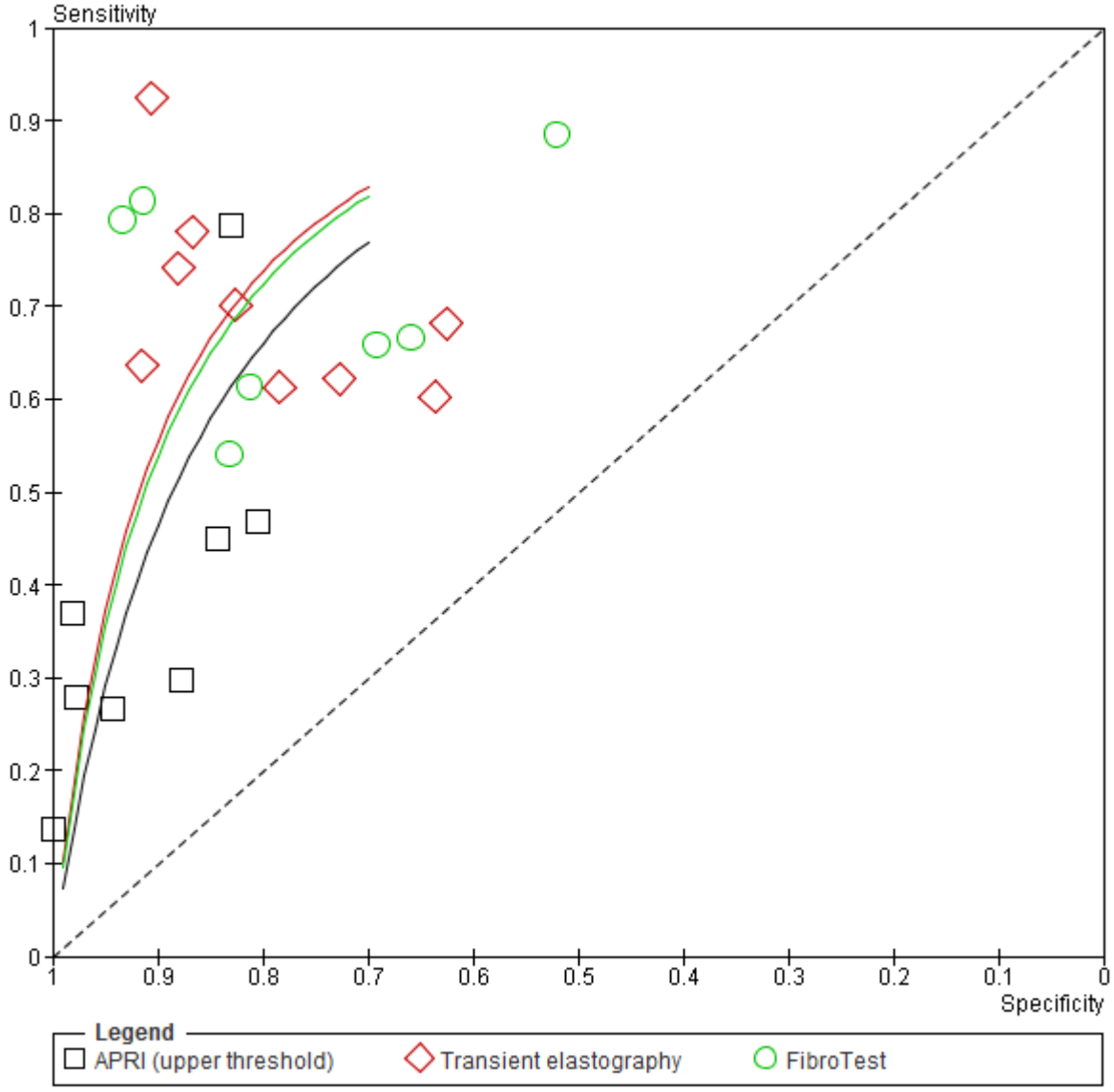


Figure 9: ROC curves for fibrosis (APRI = 0.5), by test

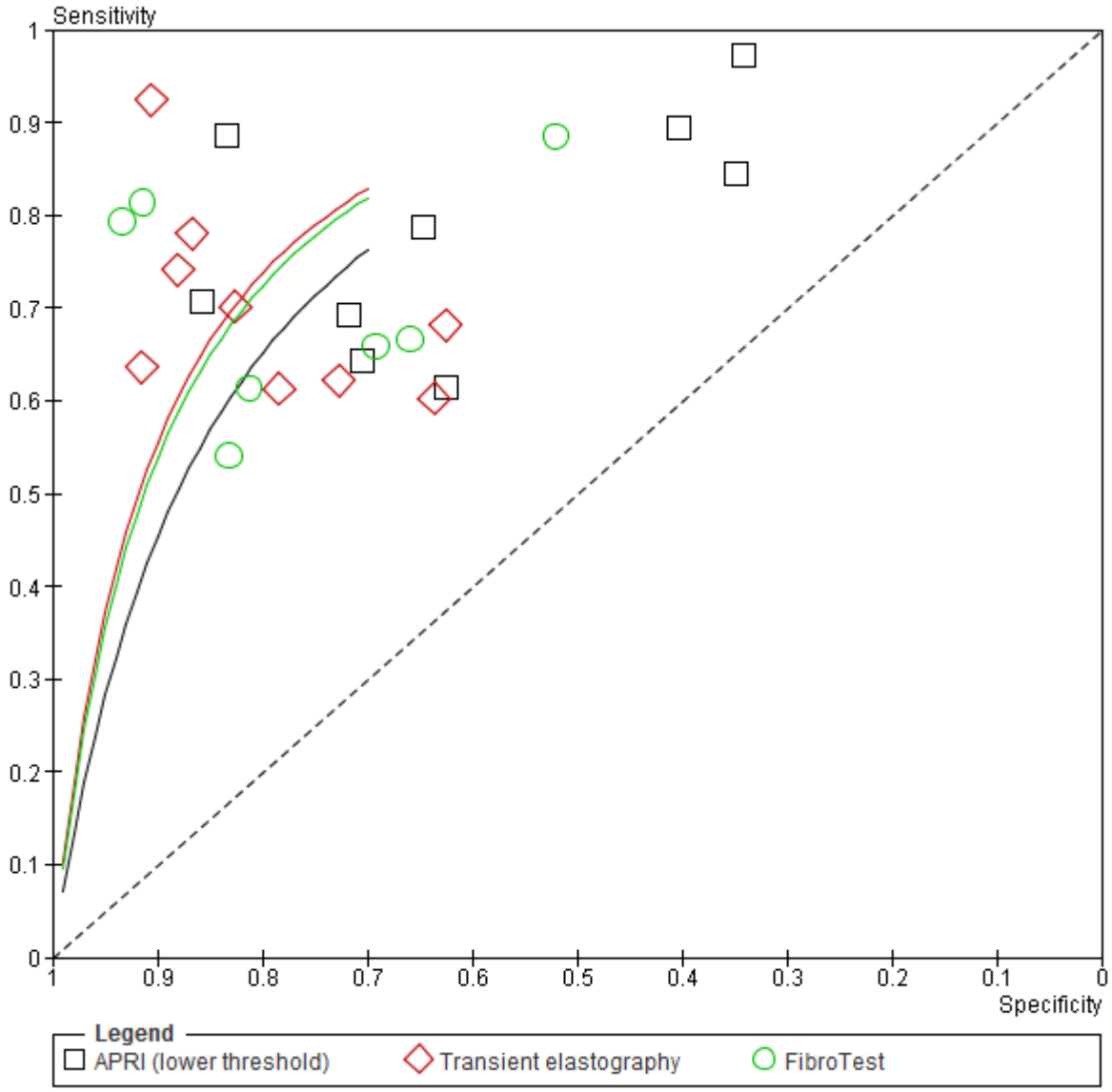


Figure 10: ROC curves with APRI mixed thresholds

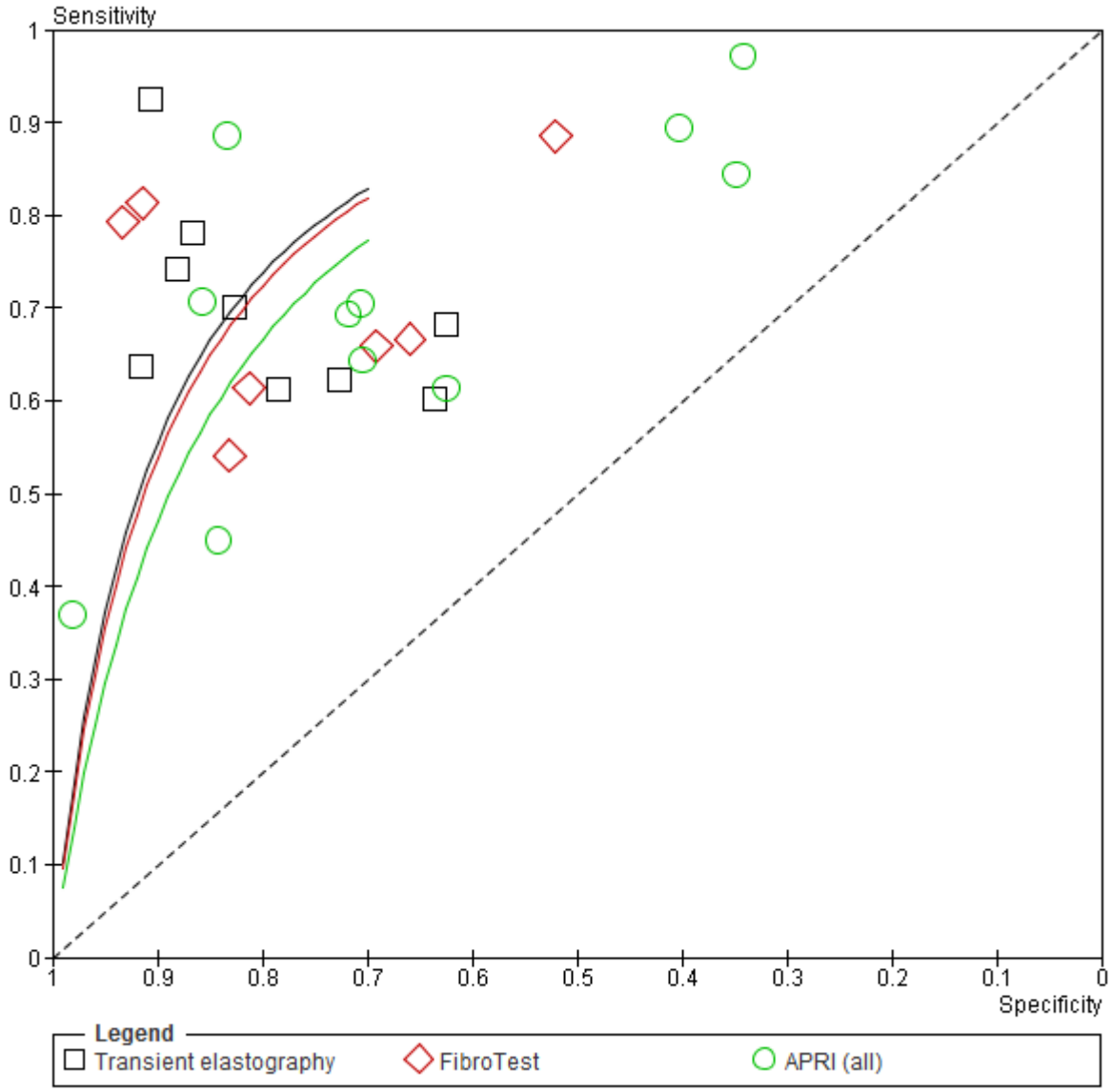


Figure 11: Sensitivity analysis – including only studies with (standard) clinically relevant thresholds to indicate heterogeneity for fibrosis

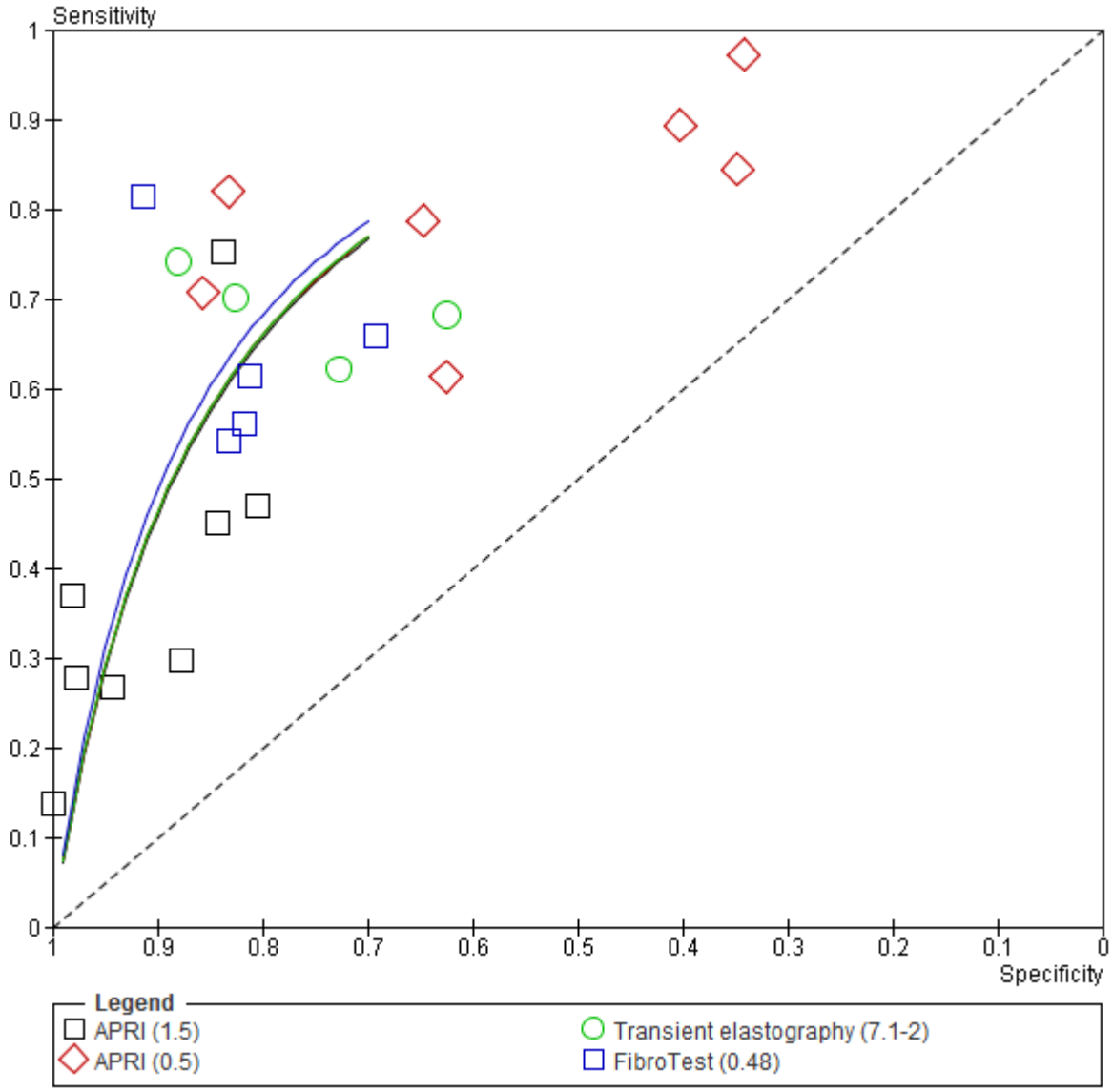
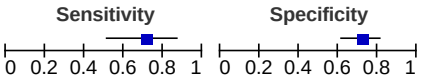


Figure 12: Summary forest plot for severe fibrosis (≥F3) – sensitivity and specificity

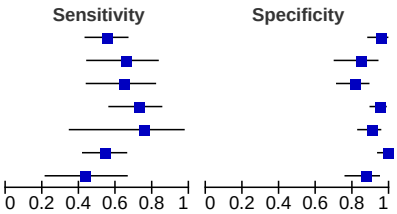
APRI

Study	TP	FP	FN	TN	Threshold	Sensitivity	Specificity
Lesmana 2011	20	25	8	64	0.27	0.71 [0.51, 0.87]	0.72 [0.61, 0.81]



Transient elastography (unit of threshold = kilopascal (kPa))

Study	TP	FP	FN	TN	Threshold	Sensitivity	Specificity
Chan 2009	43	4	35	79	11.3	0.55 [0.43, 0.66]	0.95 [0.88, 0.99]
Gaia 2011	17	7	9	37	8.9	0.65 [0.44, 0.83]	0.84 [0.70, 0.93]
Lesmana 2011	18	17	10	72	7.0	0.64 [0.44, 0.81]	0.81 [0.71, 0.88]
Marcellin 2009	31	7	12	124	10.5	0.72 [0.56, 0.85]	0.95 [0.89, 0.98]
Myers 2010	6	11	2	98	10.3	0.75 [0.35, 0.97]	0.90 [0.83, 0.95]
Wong 2010 training grp*	40	1	34	81		0.54 [0.42, 0.66]	0.99 [0.93, 1.00]
Wong2010 validation grp*	9	8	12	53		0.43 [0.22, 0.66]	0.87 [0.76, 0.94]



**Training and validation groups, threshold >9 for ALT normal group and >12 for elevated ALT group.*

Transient elastography + APRI

Study	TP	FP	FN	TN	Threshold	Sensitivity	Specificity
Lesmana 2011	20	25	8	64		0.71 [0.51, 0.87]	0.72 [0.61, 0.81]

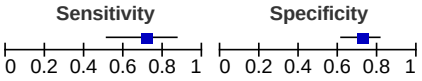


Figure 13: ROC curves for severe fibrosis, by test

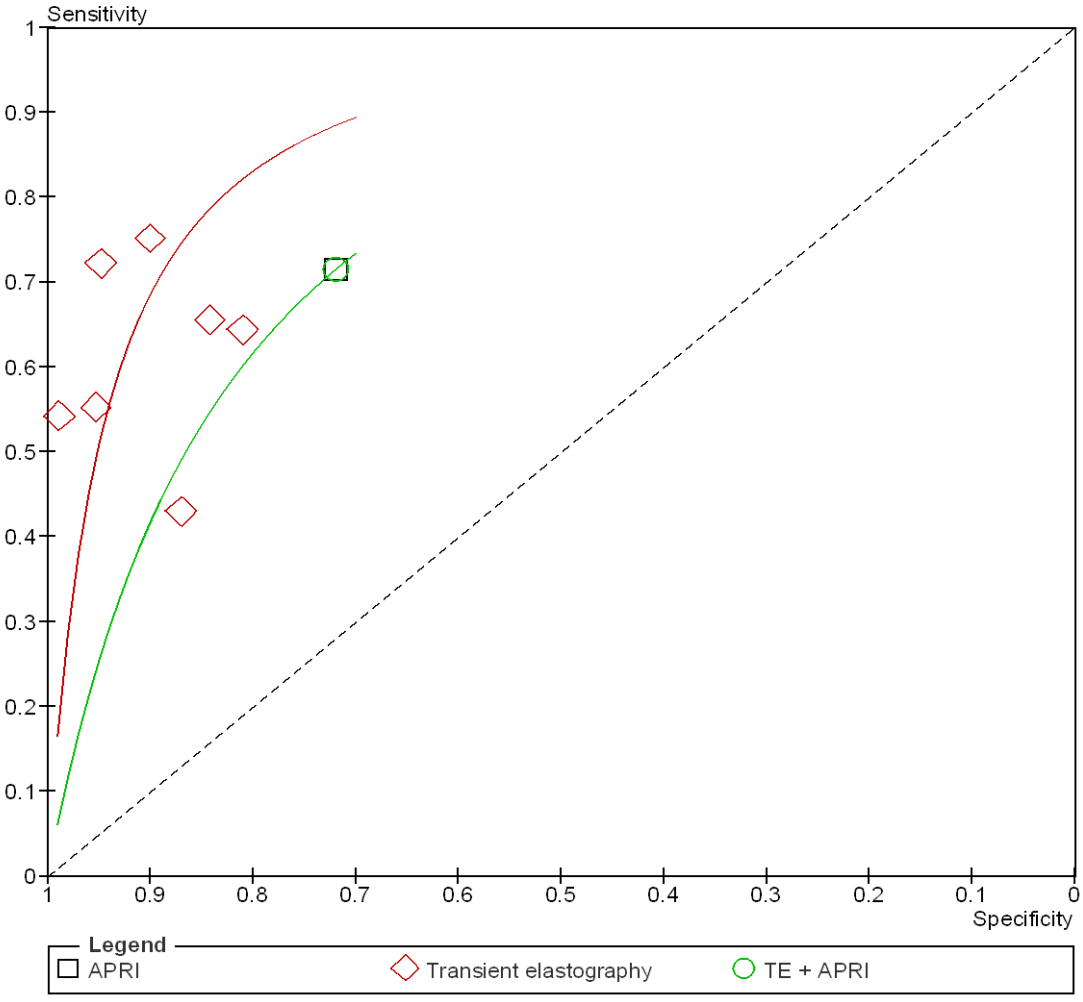


Figure 14: Summary forest plot for cirrhosis (F4) – sensitivity and specificity at standard thresholds

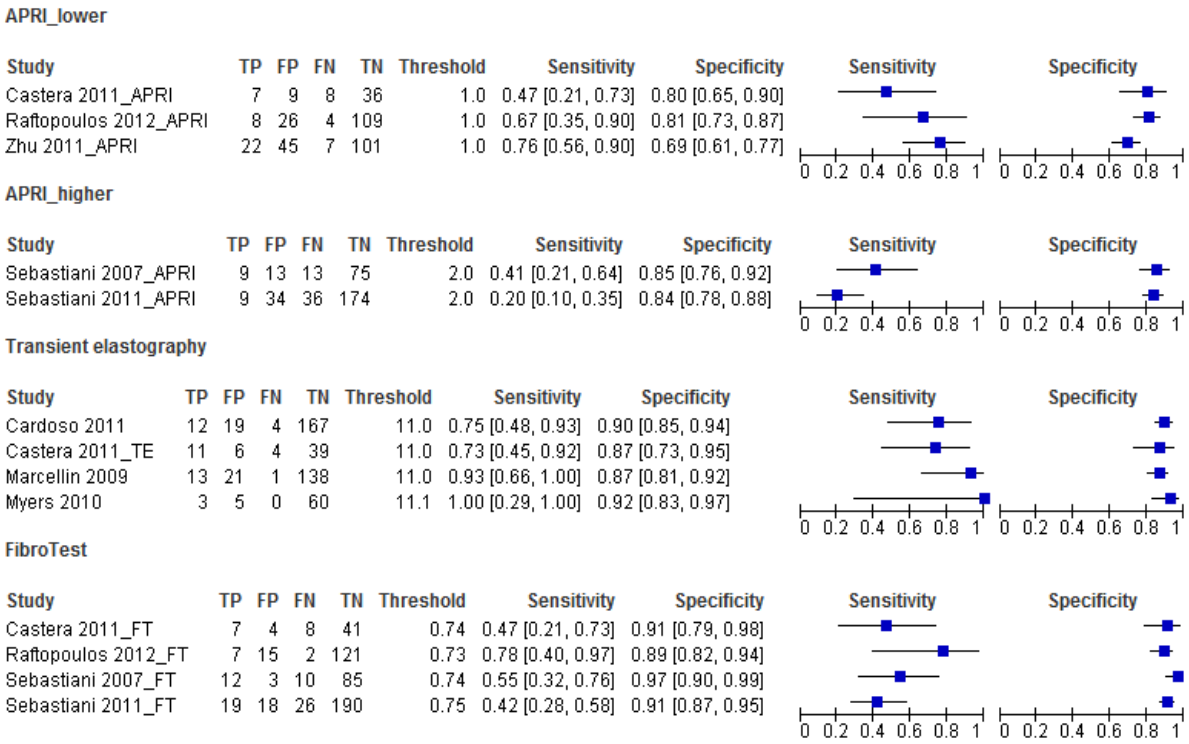


Figure 15: ROC curves for cirrhosis, by test – at optimum thresholds for each study (with APRI values combined)

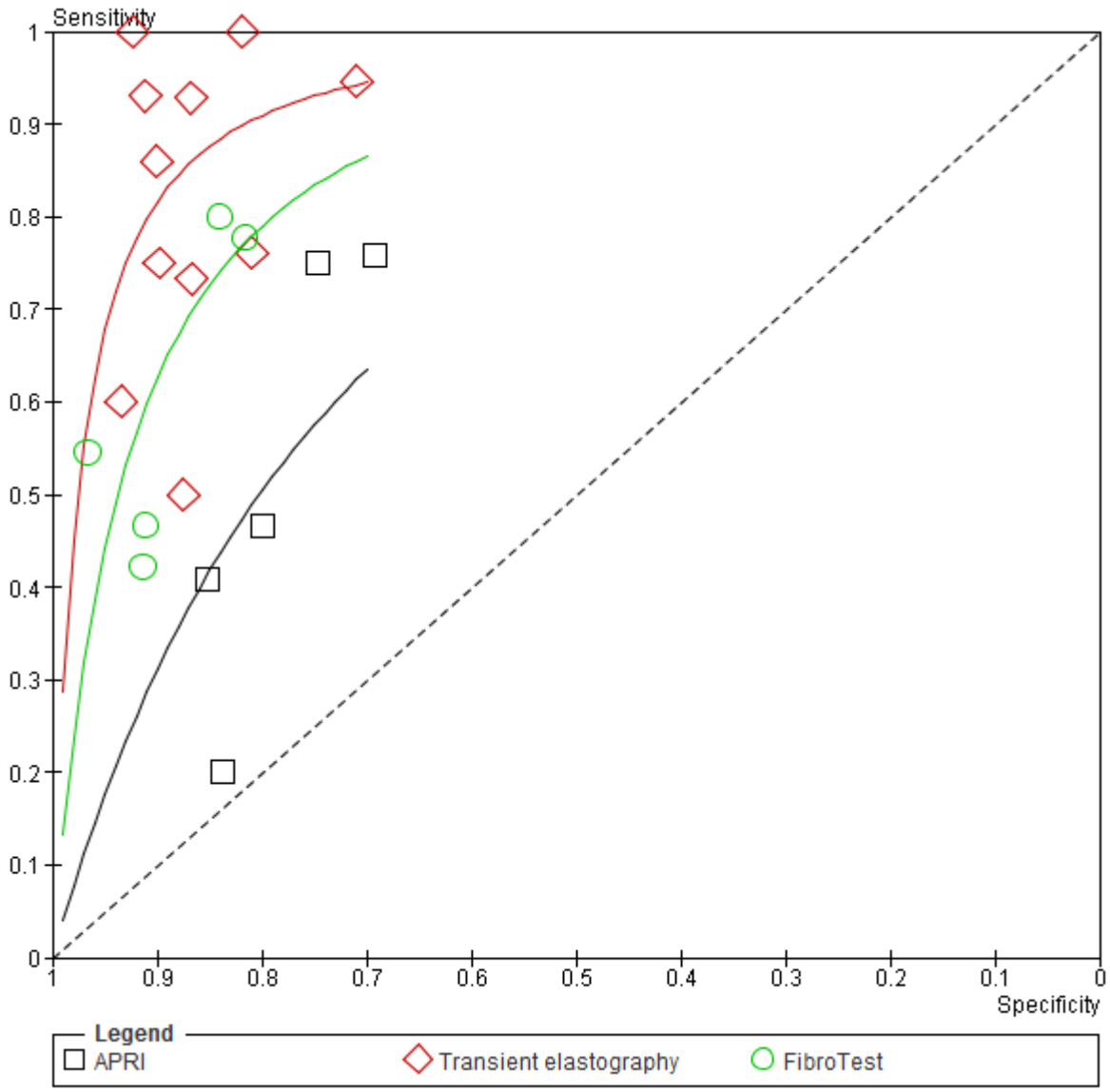
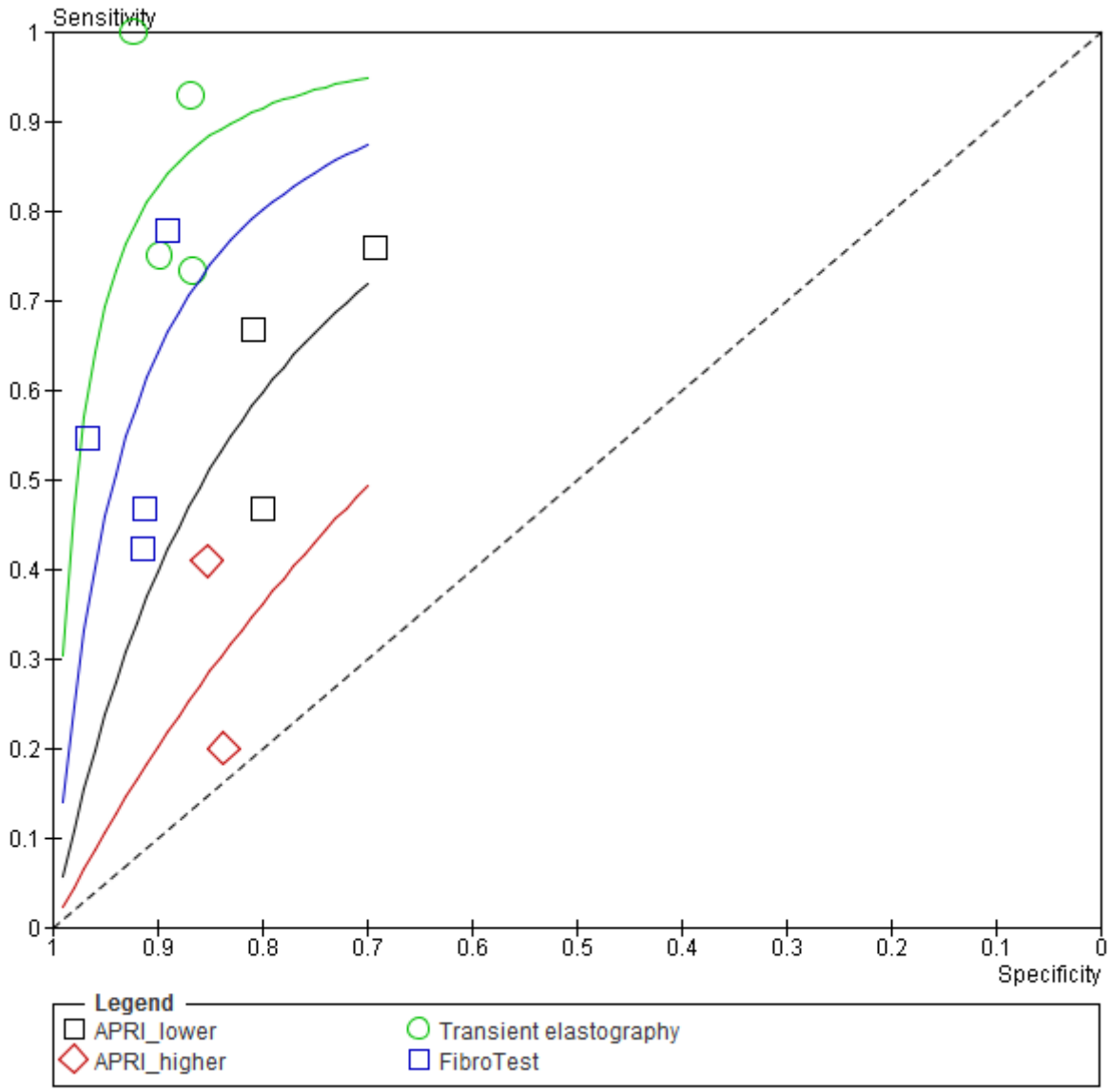


Figure 16: Sensitivity analysis – including only studies with (standard) clinically relevant thresholds to indicate heterogeneity for cirrhosis



G.2 Genotype testing

G.2.1 HBeAg positive patients with CHB on pegylated interferon treatment (α-2a and α-2b)

G.2.1.1 Genotype comparison within a single RCT comparing peg interferon versus lamivudine

Figure 17: Pegylated interferon versus lamivudine by genotype for HbAg seroconversion at 72 weeks

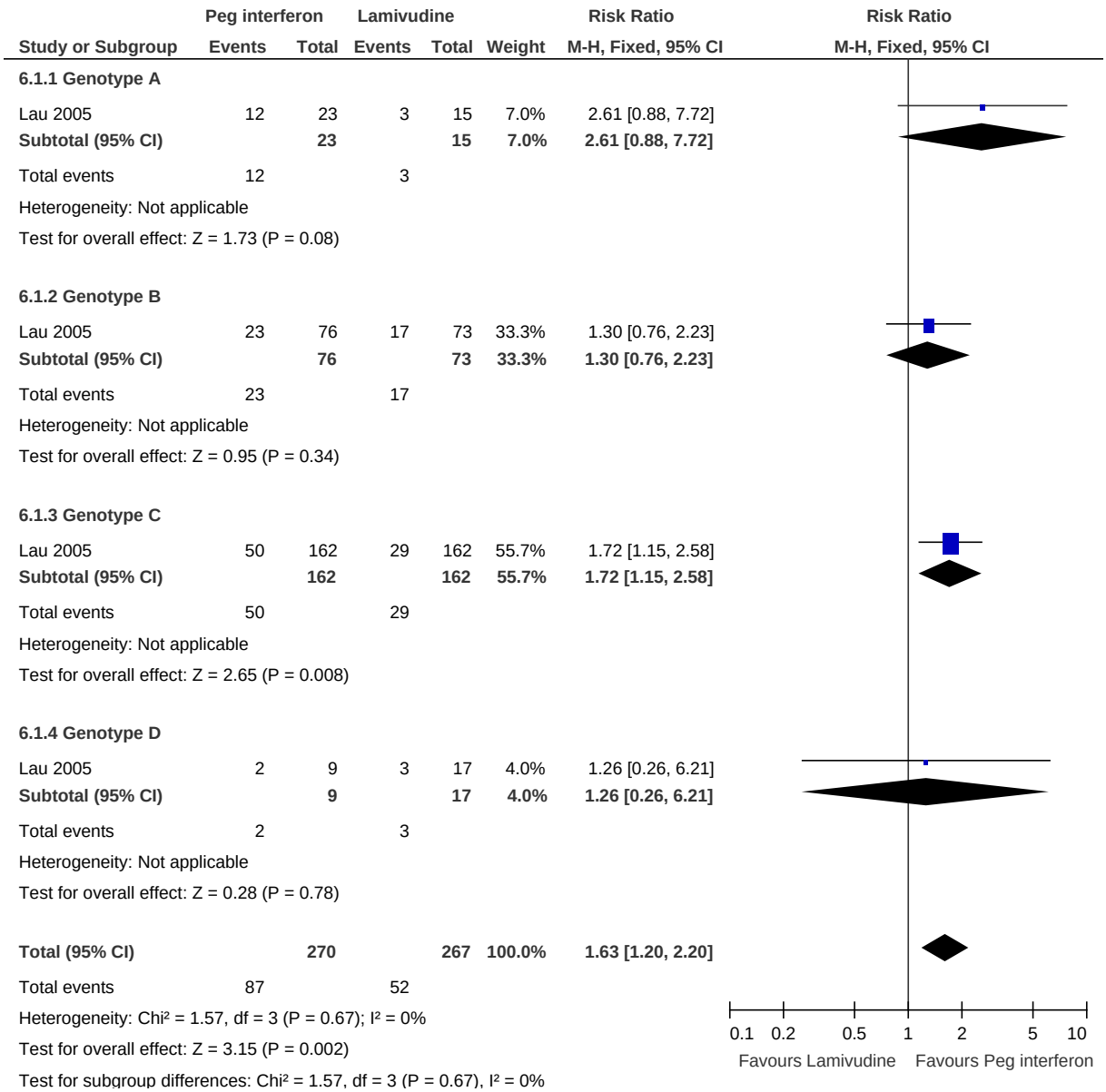
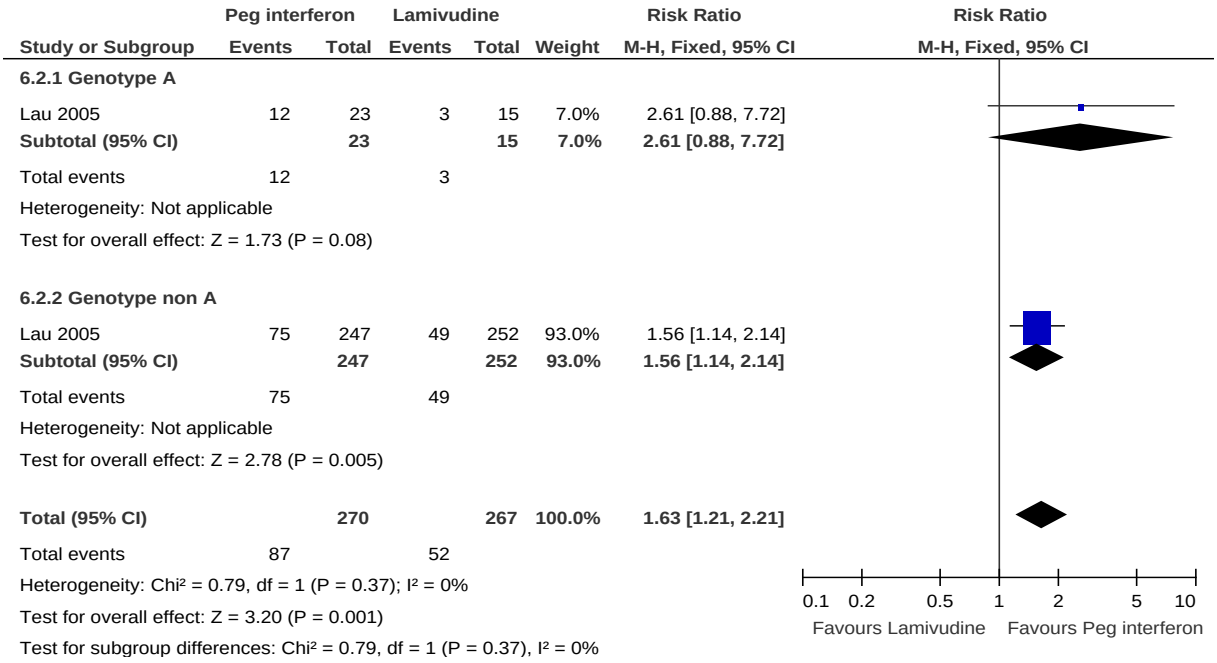
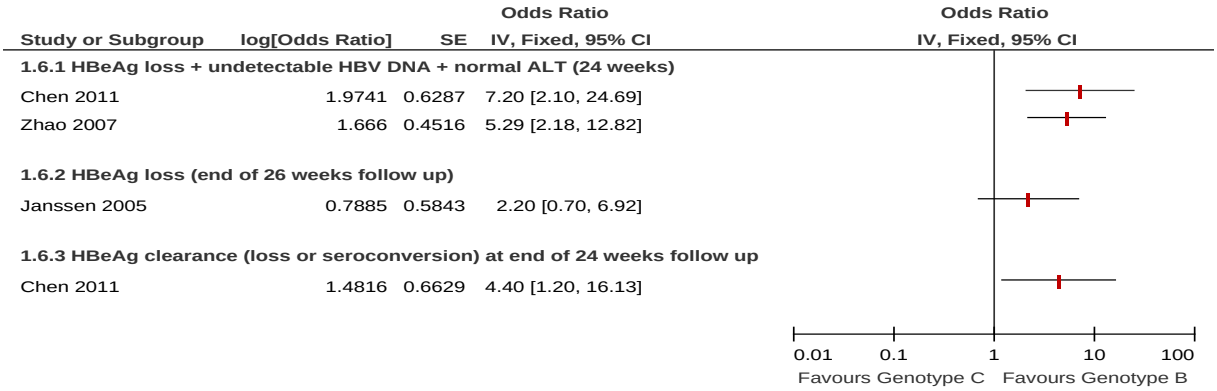


Figure 18: Pegylated interferon versus lamivudine by genotype A versus non-A for HbAg seroconversion at 72 weeks



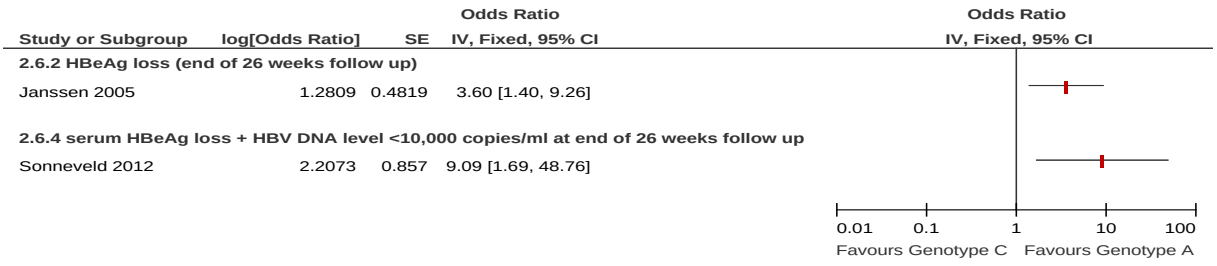
G.2.1.2 Genotype B versus C – multivariable analyses

Figure 19: response to treatment



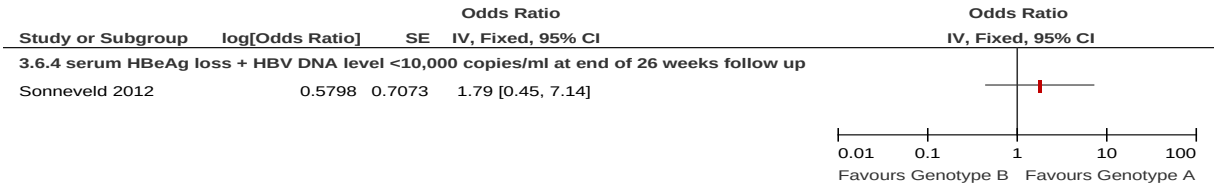
G.2.1.3 Genotype A versus C – multivariable analyses

Figure 20: response to treatment



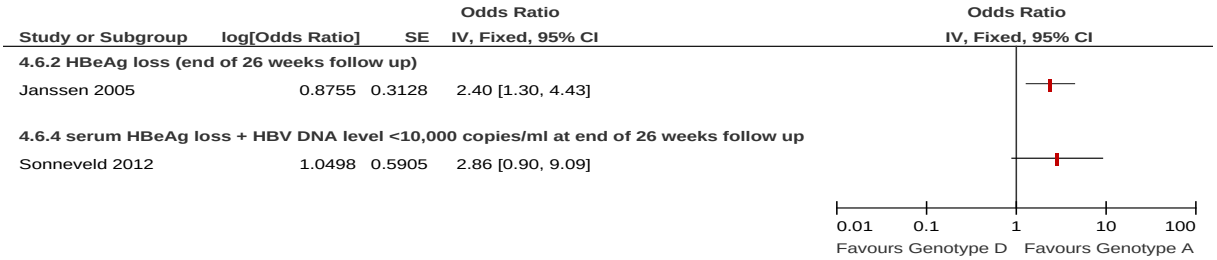
G.2.1.4 Genotype A versus B – multivariable analyses

Figure 21: response to treatment



G.2.1.5 Genotype A versus D – multivariable analyses

Figure 22: **response to treatment**



G.2.1.6 Genotype B versus C – unadjusted analyses

Figure 23: HBeAg loss (end of 26 weeks follow up)

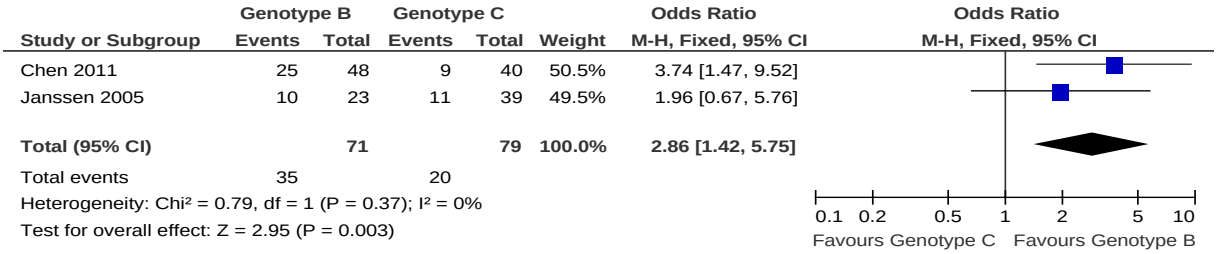


Figure 24: HBeAg seroconversion (end of 24 weeks follow up)

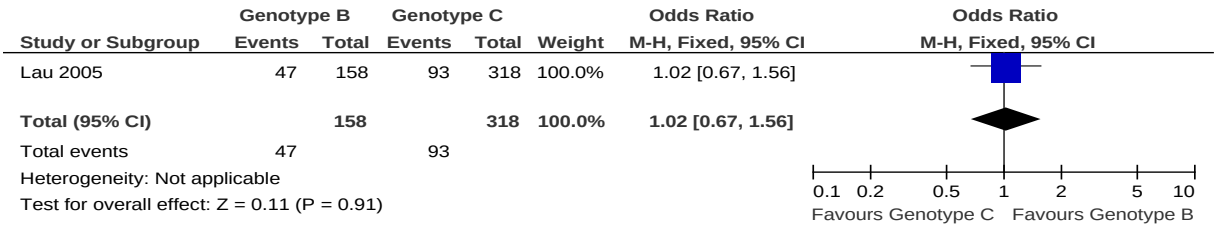


Figure 25: HBeAg and HBsAg loss (end of 26 weeks follow up)

Study or Subgroup	Genotype B Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Flink 2006A	2	23	1	39	100.0%	3.62 [0.31, 42.31]
Total (95% CI)		**23**		**39**	**100.0%**	**3.62 [0.31, 42.31]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.31)

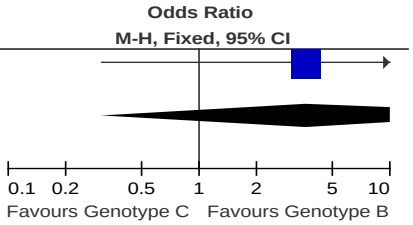


Figure 26: HBeAg loss+undetectable HBV DNA+ALT normal

Study or Subgroup	Genotype B Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen 2011	20	48	5	40	24.6%	5.00 [1.67, 15.00]
Cooksley 2003	41	125	13	61	39.8%	1.80 [0.88, 3.69]
Zhao 2007	16	60	13	170	35.6%	4.39 [1.96, 9.82]
Total (95% CI)		**233**		**271**	**100.0%**	**3.18 [1.63, 6.19]**
Total events	77		31			

Heterogeneity: Tau² = 0.16; Chi² = 3.63, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 3.40 (P = 0.0007)

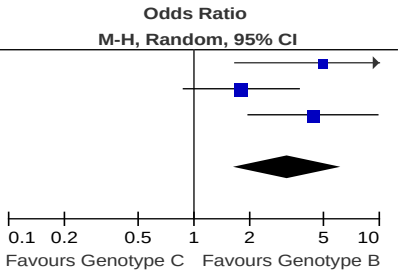
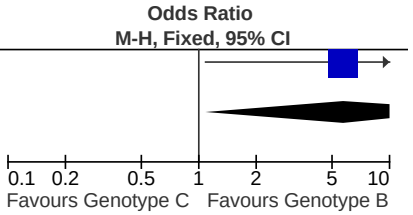


Figure 27: HBeAg loss and HBV DNA<10,000 copies/ml (end of 26 weeks follow up)

Study or Subgroup	Genotype B Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Sonneveld 2012B	5	12	3	27	100.0%	5.71 [1.09, 30.07]
Total (95% CI)		**12**		**27**	**100.0%**	**5.71 [1.09, 30.07]**
Total events	5		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)



G.2.1.7 Genotype A versus C - unadjusted analyses

Figure 28: HBeAg loss (end of 26 weeks follow up)

Study or Subgroup	Genotype A Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Janssen 2005	42	90	11	39	100.0%	2.23 [0.99, 5.01]
Total (95% CI)		**90**		**39**	**100.0%**	**2.23 [0.99, 5.01]**
Total events	42		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.93 (P = 0.05)

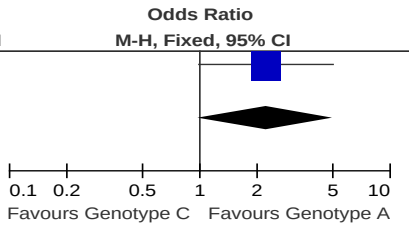


Figure 29: HBeAg seroconversion (end of 24 weeks follow up)

Study or Subgroup	Genotype A Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lau 2005	16	41	93	318	100.0%	1.55 [0.79, 3.03]
Total (95% CI)		**41**		**318**	**100.0%**	**1.55 [0.79, 3.03]**
Total events	16		93			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.20)

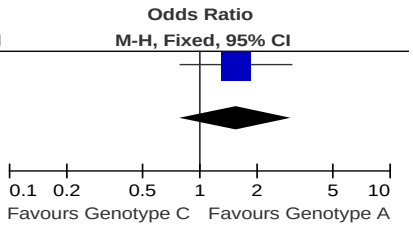


Figure 30: HBeAg and HBsAg loss (end of 26 weeks follow up)

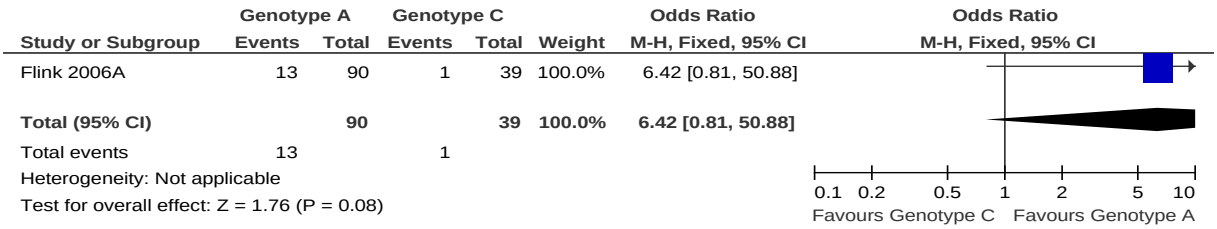
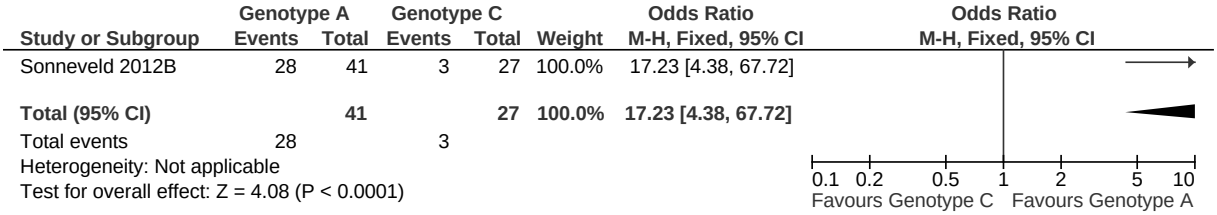


Figure 31: HBeAg loss and HBV DNA<10,000 copies/ml (end of 26 weeks follow up)



G.2.1.8 Genotype A versus B - unadjusted analyses

Figure 32: HBeAg loss (end of 26 weeks follow up)

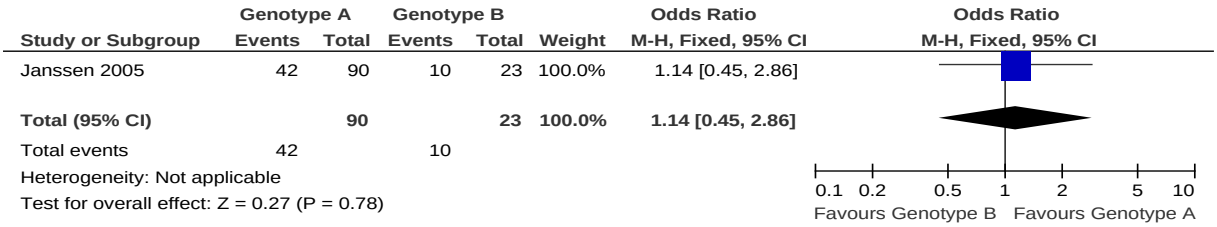


Figure 33: HBeAg seroconversion (end of 24 weeks follow up)

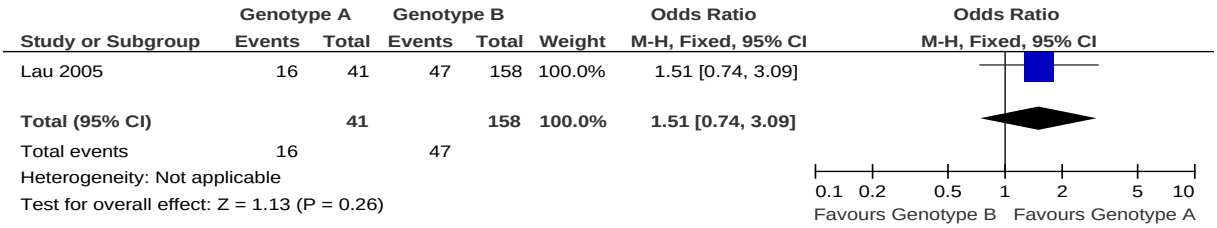


Figure 34: HBeAg and HBsAg loss (end of 26 weeks follow up)

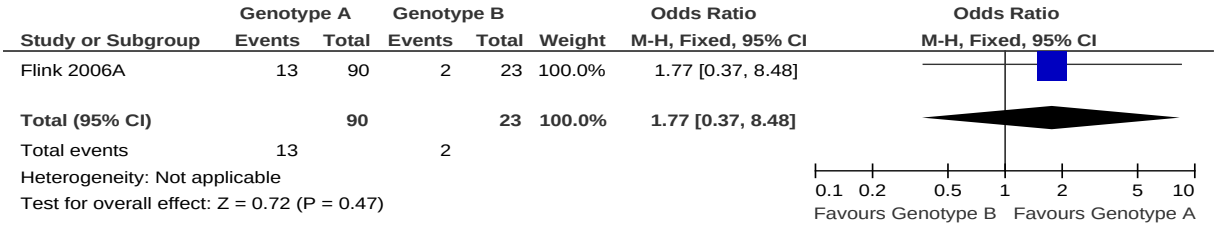
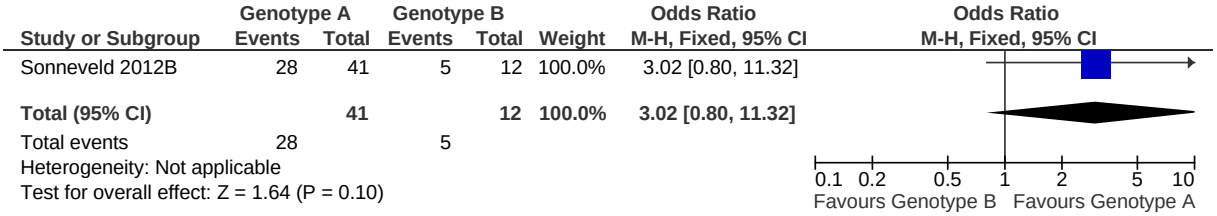


Figure 35: HBeAg loss and HBV DNA<10,000 copies/ml (end of 26 weeks follow up)



G.2.1.9 Genotype A versus D - unadjusted analyses

Figure 36: HBeAg loss (end of 26 weeks follow up)

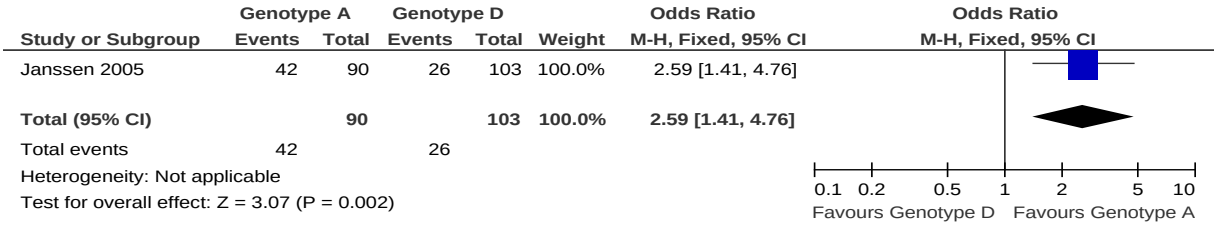


Figure 37: HBeAg loss and HBV DNA<10,000 copies/ml (end of 26 weeks follow up)

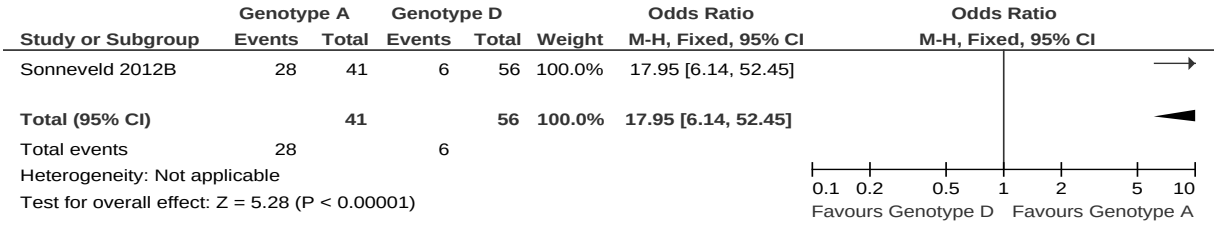
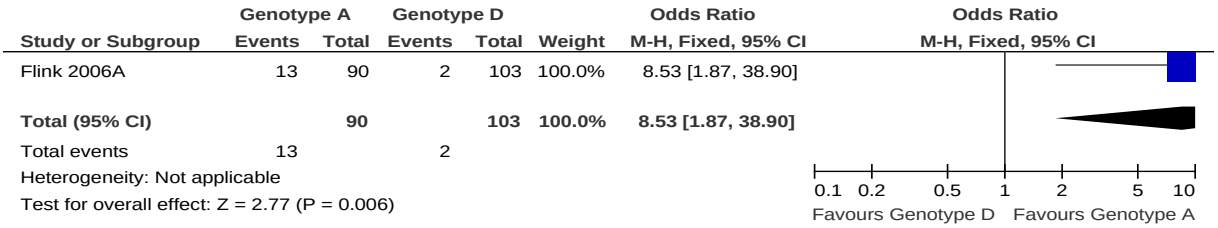


Figure 38: HBeAg and HBsAg loss (end of 26 weeks follow up)



G.2.1.10 Genotype A versus D (with flares) - unadjusted analyses

Figure 39: HBeAg loss (end of 26 weeks follow up)

G.2.1.11 Genotype A versus D (initial responders) - unadjusted analyses

Figure 40: HBeAg loss (mean 3 years follow up)

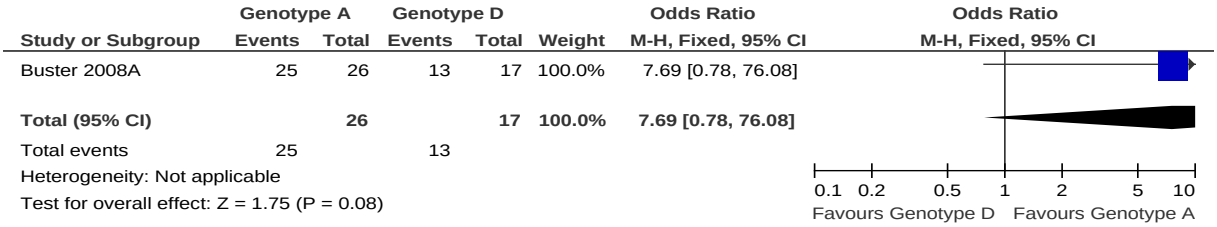
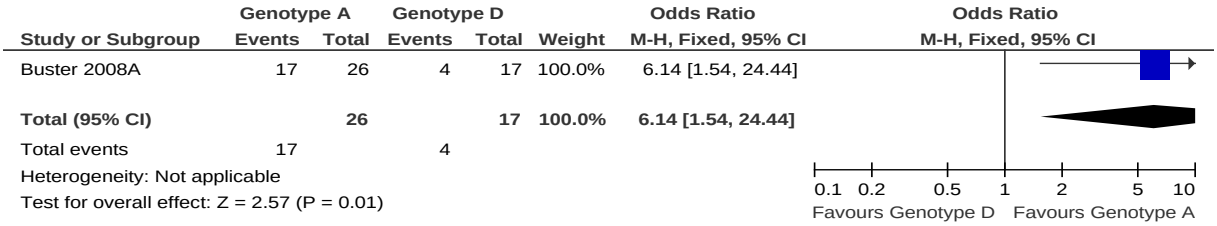


Figure 41: HBV DNA<400 copies/ml (mean 3 years follow up)



G.2.1.12 Genotype B versus D - unadjusted analyses

Figure 42: HBeAg loss (end of 26 weeks follow up)

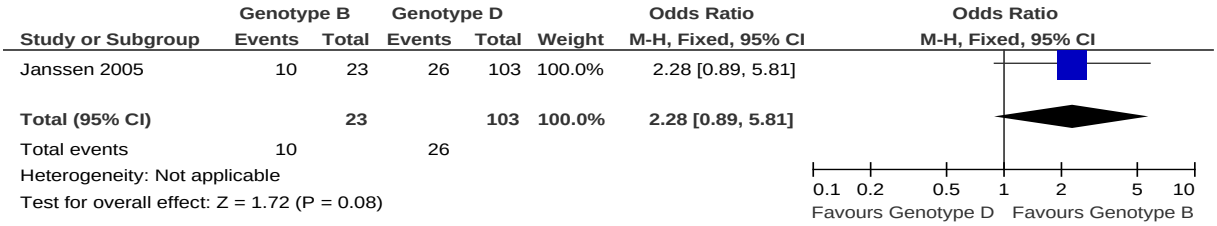


Figure 43: HBeAg loss and HBV DNA<10,000 copies/ml (end of 26 weeks follow up)

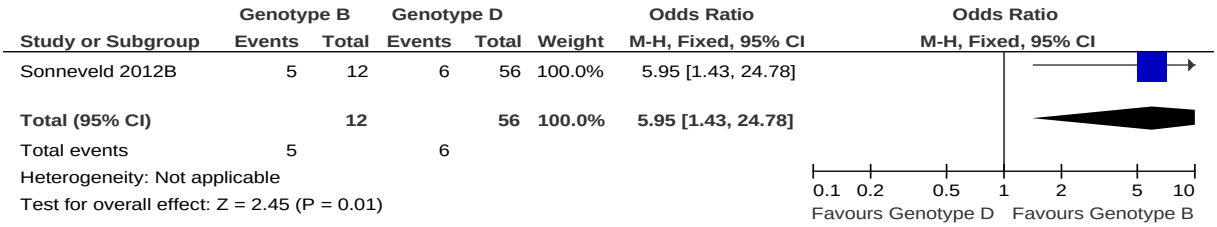
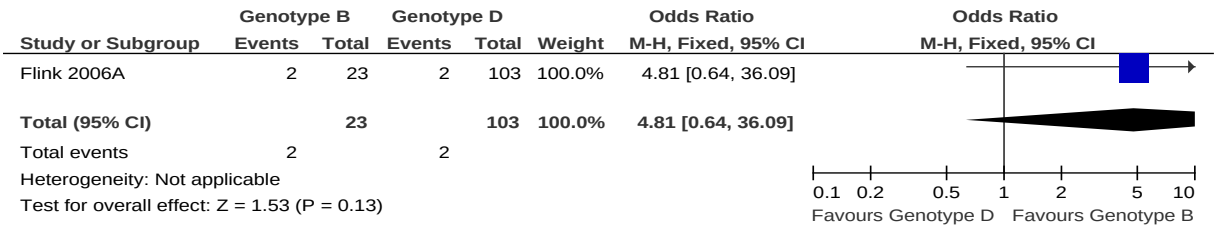


Figure 44: HBeAg and HBsAg loss (end of 26 weeks follow up)



G.2.1.13 Genotype C versus D - unadjusted analyses

Figure 45: HBeAg loss (end of 26 weeks follow up)

Study or Subgroup	Genotype C Events	Genotype C Total	Genotype D Events	Genotype D Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Janssen 2005	11	39	26	103	100.0%	1.16 [0.51, 2.66]
Total (95% CI)		**39**		**103**	**100.0%**	**1.16 [0.51, 2.66]**
Total events	11		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

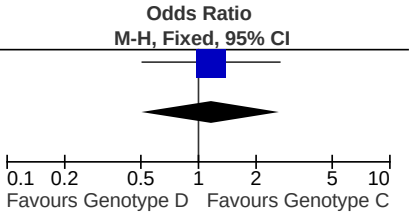


Figure 46: HBeAg and HBsAg loss (end of 26 weeks follow up

Study or Subgroup	Genotype C Events	Genotype C Total	Genotype D Events	Genotype D Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Flink 2006A	1	39	2	103	100.0%	1.33 [0.12, 15.08]
Total (95% CI)		**39**		**103**	**100.0%**	**1.33 [0.12, 15.08]**
Total events	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

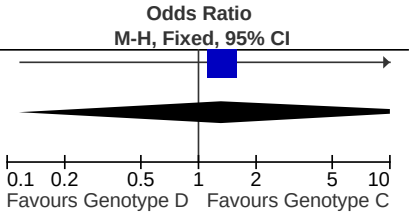
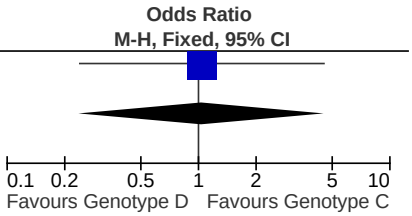


Figure 47: HBeAg loss and HBV DNA<10,000 copies/ml (end of 26 weeks follow up)

Study or Subgroup	Genotype C Events	Genotype C Total	Genotype D Events	Genotype D Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Sonneveld 2012B	3	27	6	56	100.0%	1.04 [0.24, 4.53]
Total (95% CI)		**27**		**56**	**100.0%**	**1.04 [0.24, 4.53]**
Total events	3		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)

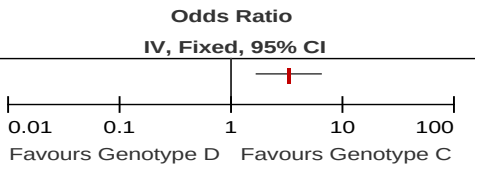


G.2.2 HBeAg negative patients with CHB on pegylated interferon treatment (α-2a and α-2b)

G.2.2.1 Genotype C versus D – multivariable analysis

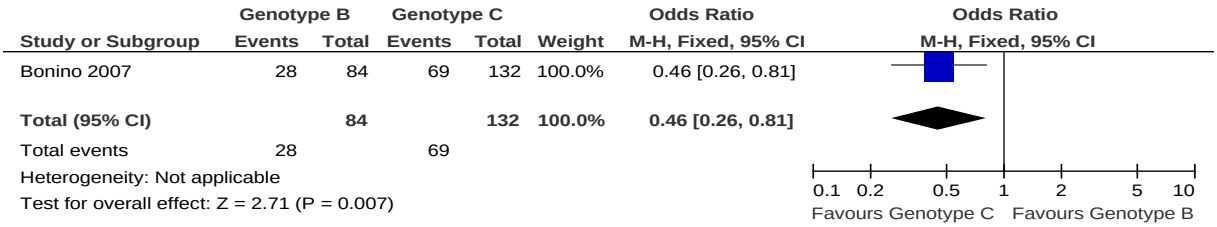
Figure 48: HBeAg loss and HBV DNA<10,000 copies/ml (end of 26 weeks follow up)

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Fixed, 95% CI
Bonino 2007	1.1939	0.3384	3.30 [1.70, 6.41]



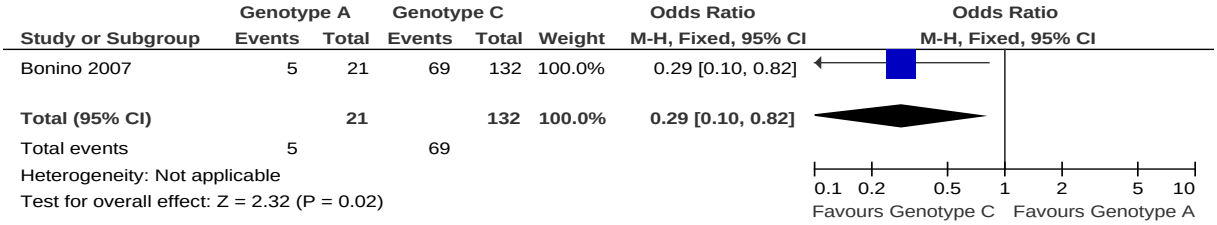
G.2.2.2 Genotype B versus C – unadjusted analysis

Figure 49: HBV DNA<20,000 copies/ml+ALT normal



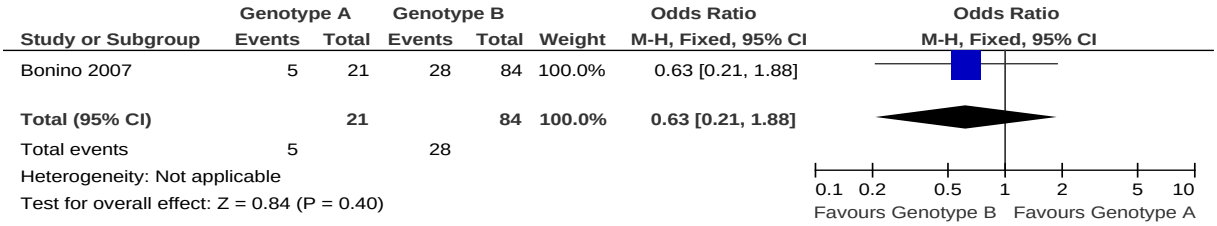
G.2.2.3 Genotype A versus C - unadjusted analyses

Figure 50: HBV DNA<20,000 copies/ml+ALT normal



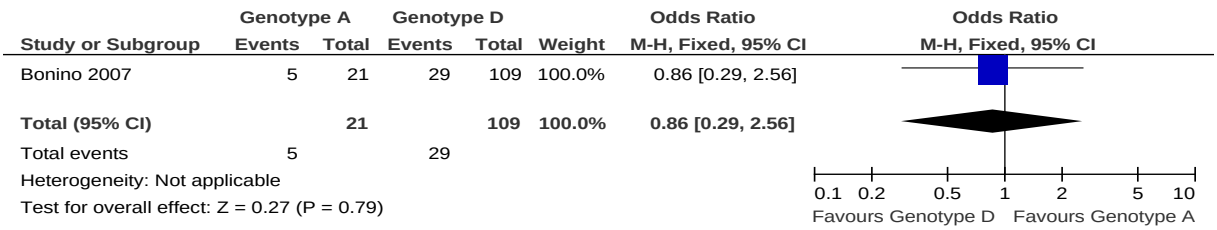
G.2.2.4 Genotype A versus B - unadjusted analyses

Figure 51: HBV DNA<20,000 copies/ml+ALT normal



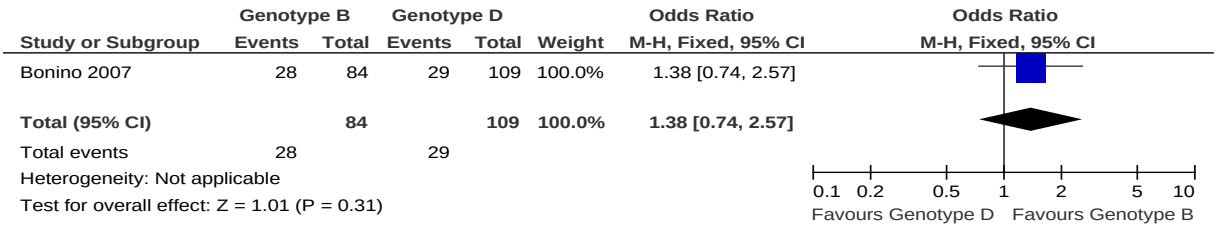
G.2.2.5 Genotype A versus D - unadjusted analyses

Figure 52: HBV DNA<20,000 copies/ml+ALT normal



G.2.2.6 Genotype B versus D - unadjusted analyses

Figure 53: HBV DNA<20,000 copies/ml+ALT normal



G.2.3 HBeAg positive patients with CHB on lamivudine treatment

G.2.3.1 Genotype B versus C – multivariable analyses

Figure 54: Complete response (ALT normal + HBV DNA undetectable + seroconversion)

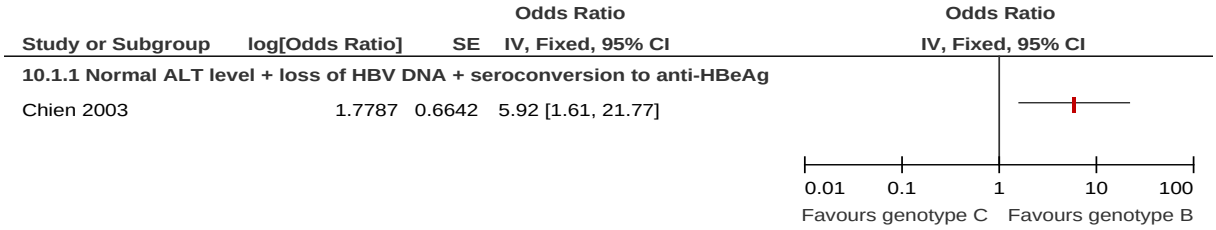
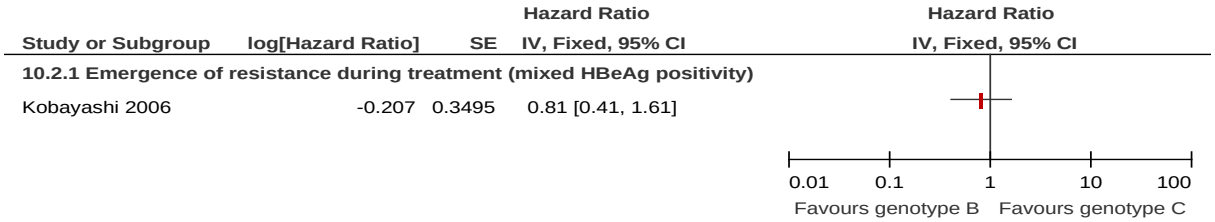
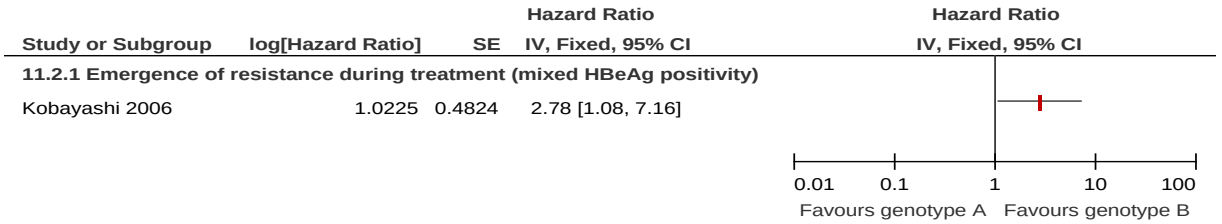


Figure 55: Resistance (mixed HBeAg positivity)



G.2.3.2 Genotype A versus B – multivariable analyses

Figure 56: Resistance (mixed HBeAg positivity)



G.2.3.3 Genotype B versus C – unadjusted analyses

Figure 57: HBeAg seroconversion (24 weeks -15 months follow up)

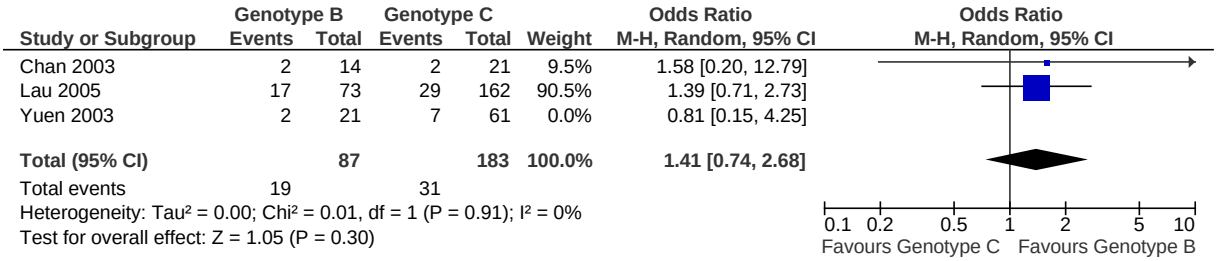


Figure 58: Resistance

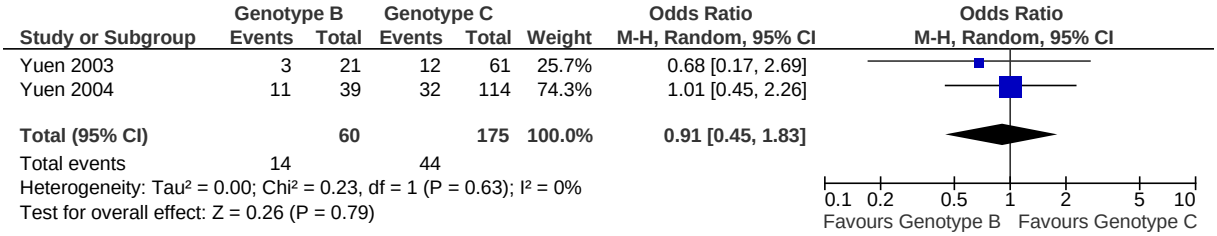
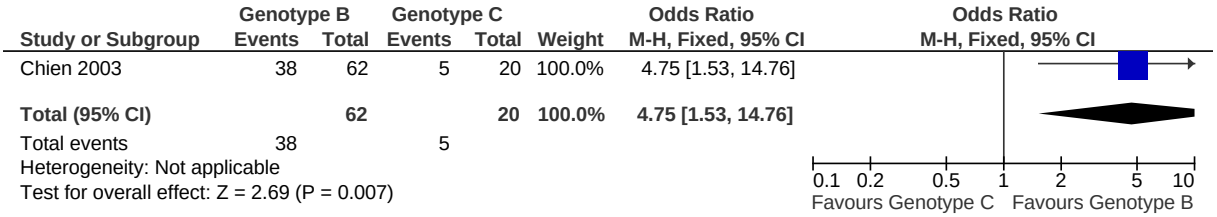
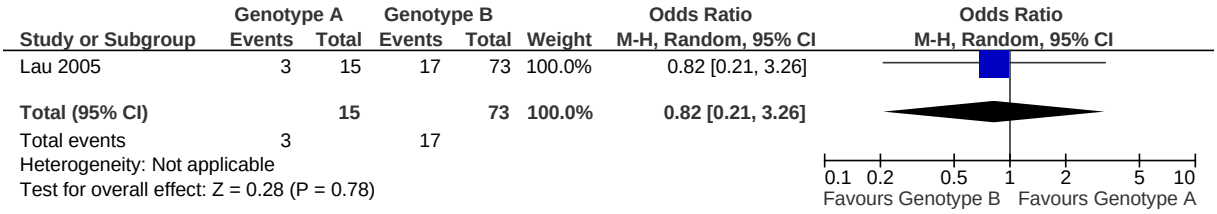


Figure 59: ALT normalization and undetectable HBV DNA and HBeAg seroconversion



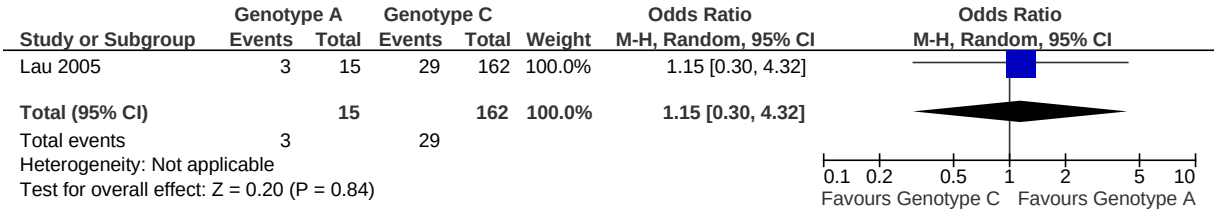
G.2.3.4 Genotype A versus B

Figure 60: HBeAg seroconversion (24 weeks follow up)



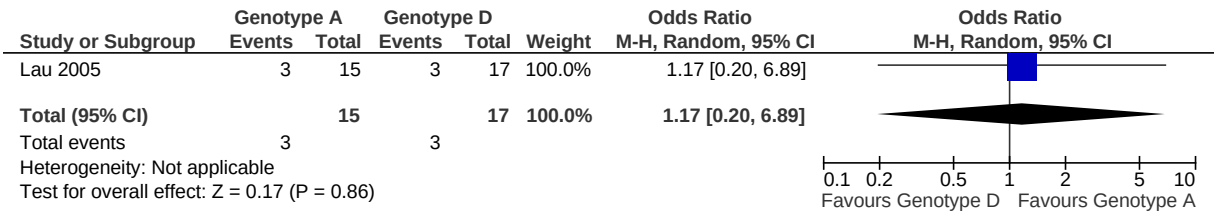
G.2.3.5 Genotype A versus C

Figure 61: HBeAg seroconversion (24 weeks follow up)



G.2.3.6 Genotype A versus D

Figure 62: HBeAg seroconversion (24 weeks follow up)

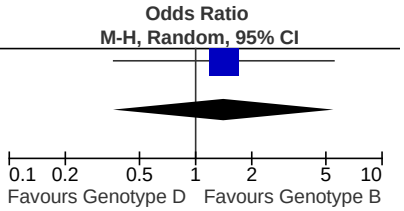


G.2.3.7 Genotype B versus D

Figure 63: HBeAg seroconversion (24 weeks follow up)

Study or Subgroup	Genotype B Events	Total	Genotype D Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Lau 2005	17	73	3	17	100.0%	1.42 [0.36, 5.52]
Total (95% CI)		**73**		**17**	**100.0%**	**1.42 [0.36, 5.52]**
Total events	17		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)

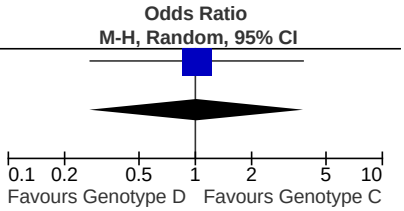


G.2.3.8 Genotype C versus D

Figure 64: HBeAg seroconversion (24 weeks follow up)

Study or Subgroup	Genotype C Events	Total	Genotype D Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Lau 2005	29	162	3	17	100.0%	1.02 [0.27, 3.77]
Total (95% CI)		**162**		**17**	**100.0%**	**1.02 [0.27, 3.77]**
Total events	29		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)



G.2.4 HBeAg negative patients with CHB on lamivudine treatment

G.2.4.1 Genotype B versus C - unadjusted analyses

Figure 65: ALT normal and undetectable HBV DNA

Study or Subgroup	Genotype B Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bonino 2007	19	49	15	57	100.0%	1.77 [0.78, 4.04]
Total (95% CI)		**49**		**57**	**100.0%**	**1.77 [0.78, 4.04]**
Total events	19		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)

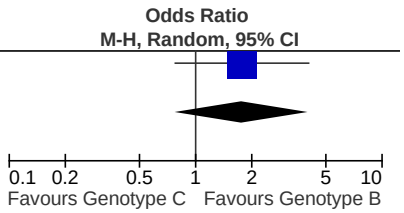


Figure 66: ALT normalization (after 1 year of treatment)

Study or Subgroup	Genotype B Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Suzuki 2003	17	17	89	102	100.0%	5.28 [0.30, 93.00]
Total (95% CI)		**17**		**102**	**100.0%**	**5.28 [0.30, 93.00]**
Total events	17		89			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.26)

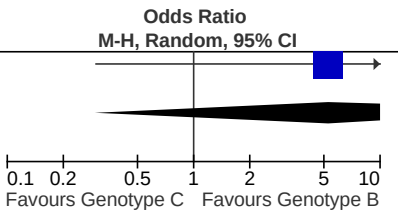


Figure 67: ALT normalization (after 2 years of treatment)

Study or Subgroup	Genotype B Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Suzuki 2003	10	11	40	50	100.0%	2.50 [0.29, 21.88]
Total (95% CI)		**11**		**50**	**100.0%**	**2.50 [0.29, 21.88]**
Total events	10		40			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)

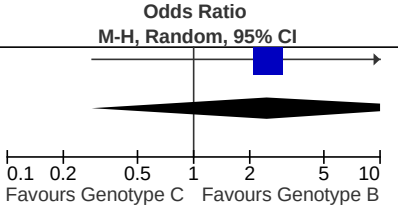


Figure 68: undetectable HBV DNA (<0.7 x 106 copies/ml) (after 1 year of treatment)

Study or Subgroup	Genotype B Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Suzuki 2003	14	15	95	101	100.0%	0.88 [0.10, 7.90]
Total (95% CI)		**15**		**101**	**100.0%**	**0.88 [0.10, 7.90]**
Total events	14		95			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)

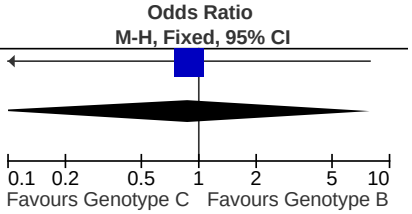


Figure 69: undetectable HBV DNA (<0.7 x 106 copies/ml) (after 2 years of treatment)

Study or Subgroup	Genotype B Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Suzuki 2003	10	11	46	49	100.0%	0.65 [0.06, 6.94]
Total (95% CI)		**11**		**49**	**100.0%**	**0.65 [0.06, 6.94]**
Total events	10		46			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.72)

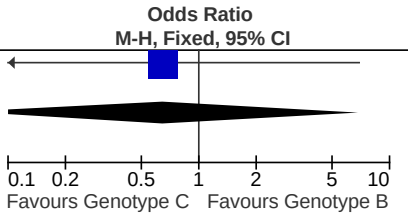


Figure 70: Resistance (1 yr of treatment)

Study or Subgroup	Genotype B Events	Total	Genotype C Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Akuta 2003A	0	17	7	79	100.0%	0.28 [0.02, 5.07]
Total (95% CI)		**17**		**79**	**100.0%**	**0.28 [0.02, 5.07]**
Total events	0		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.39)

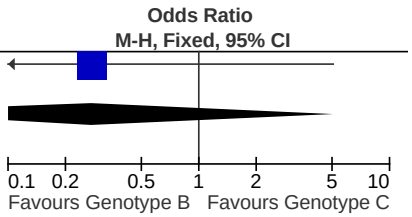


Figure 71: Resistance (2 years of treatment)

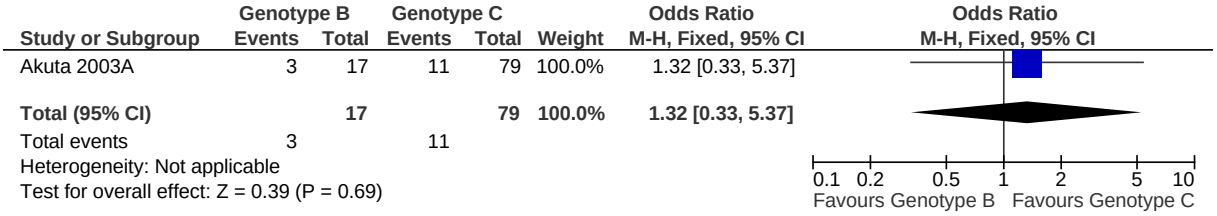
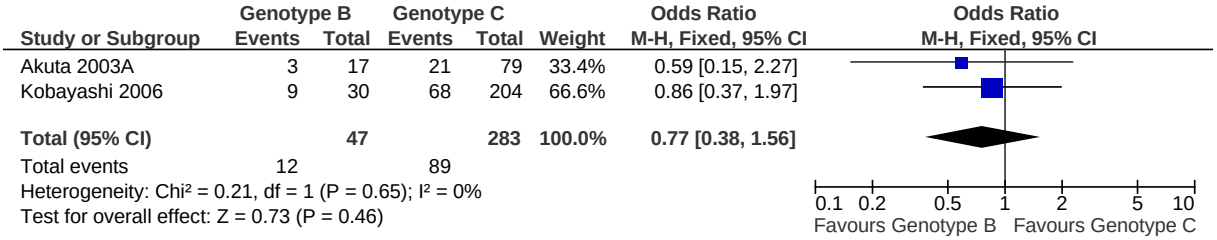
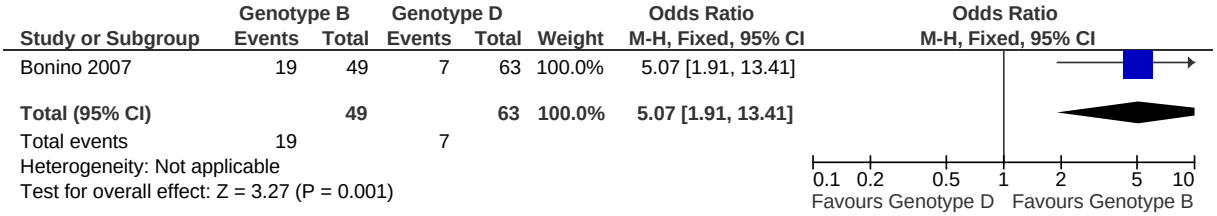


Figure 72: Resistance (3 years of treatment)



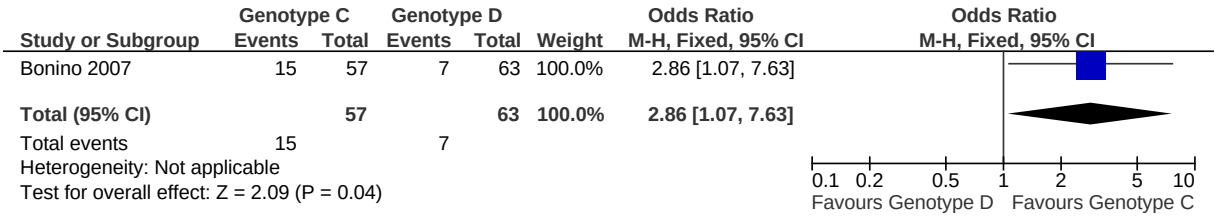
G.2.4.2 Genotype B versus D

Figure 73: ALT normal and undetectable HBV DNA



G.2.4.3 Genotype C versus D

Figure 74: ALT normal and undetectable HBV DNA



G.3 Antiviral treatment

G.3.1 Monotherapies and combinations

G.3.1.1 Pharmacological monotherapy and combination therapies in achieving remission of the action of CHB infection for HBeAg positive adults

Nucleos(t)ide naïve

Comparison of adefovir versus placebo (HBeAg positive)

Figure 75: **Mean reduction in HBV DNA (log copies/mL, week 48)**

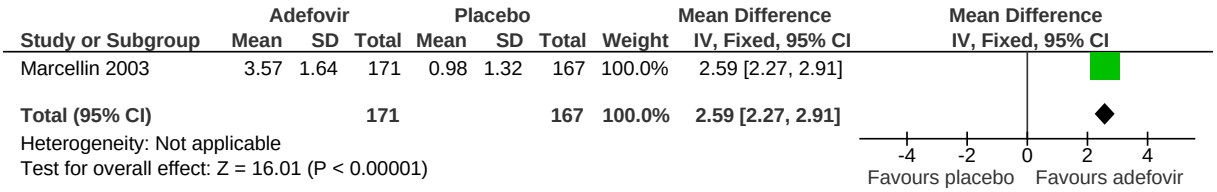


Figure 76: **% of people with continuing undetectable HBV DNA (<400 copies/ml) (week 48)**

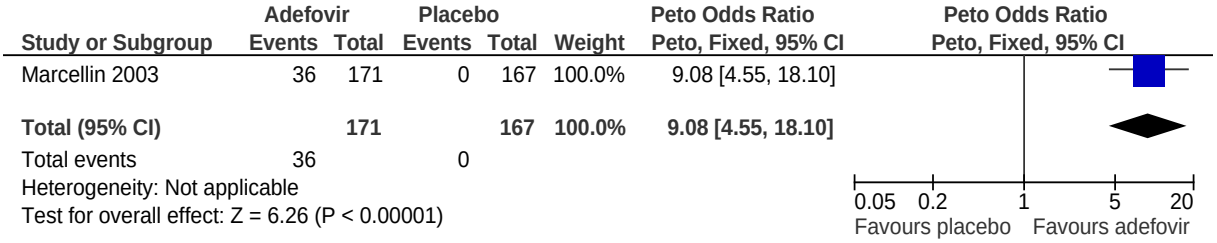


Figure 77: **% of people with HBeAg loss (week 48)**

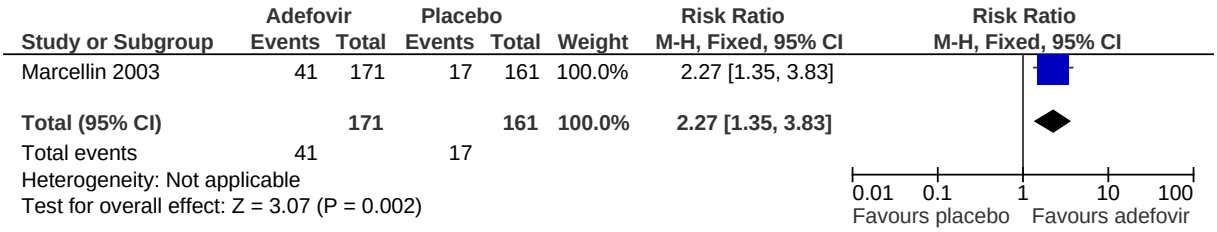


Figure 78: **% of people with HBeAg seroconversion (week 48)**

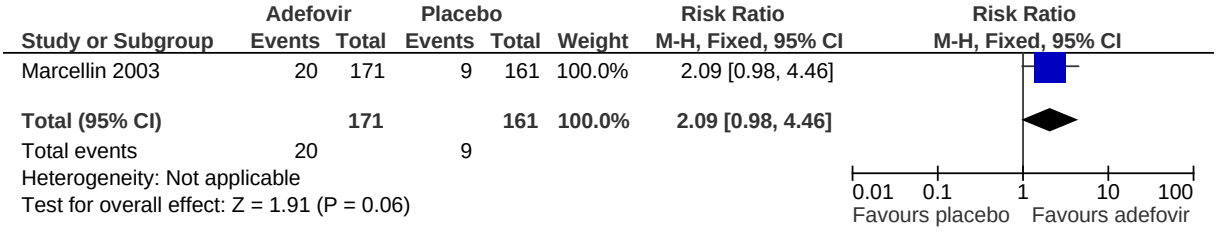


Figure 79: **% of people with ALT normalisation (week 48)**

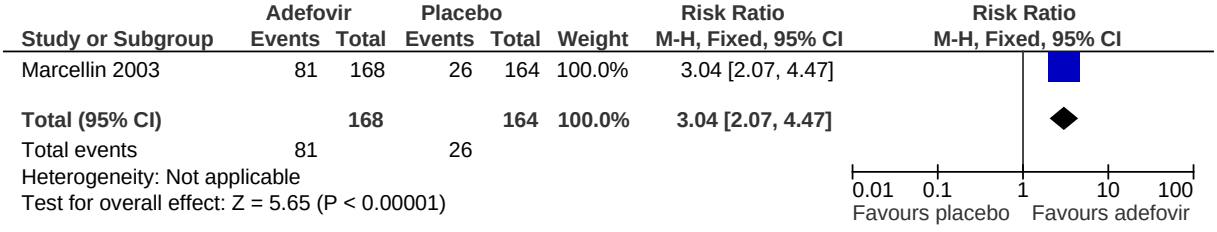
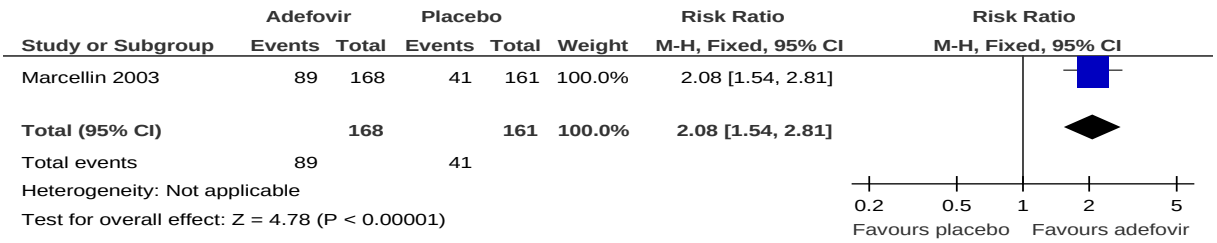


Figure 80: **% of people with histologic improvement (week 48)**



Comparison of lamivudine versus placebo (HBeAg positive)

Figure 81: **% of people with undetectable HBV DNA at end of treatment**

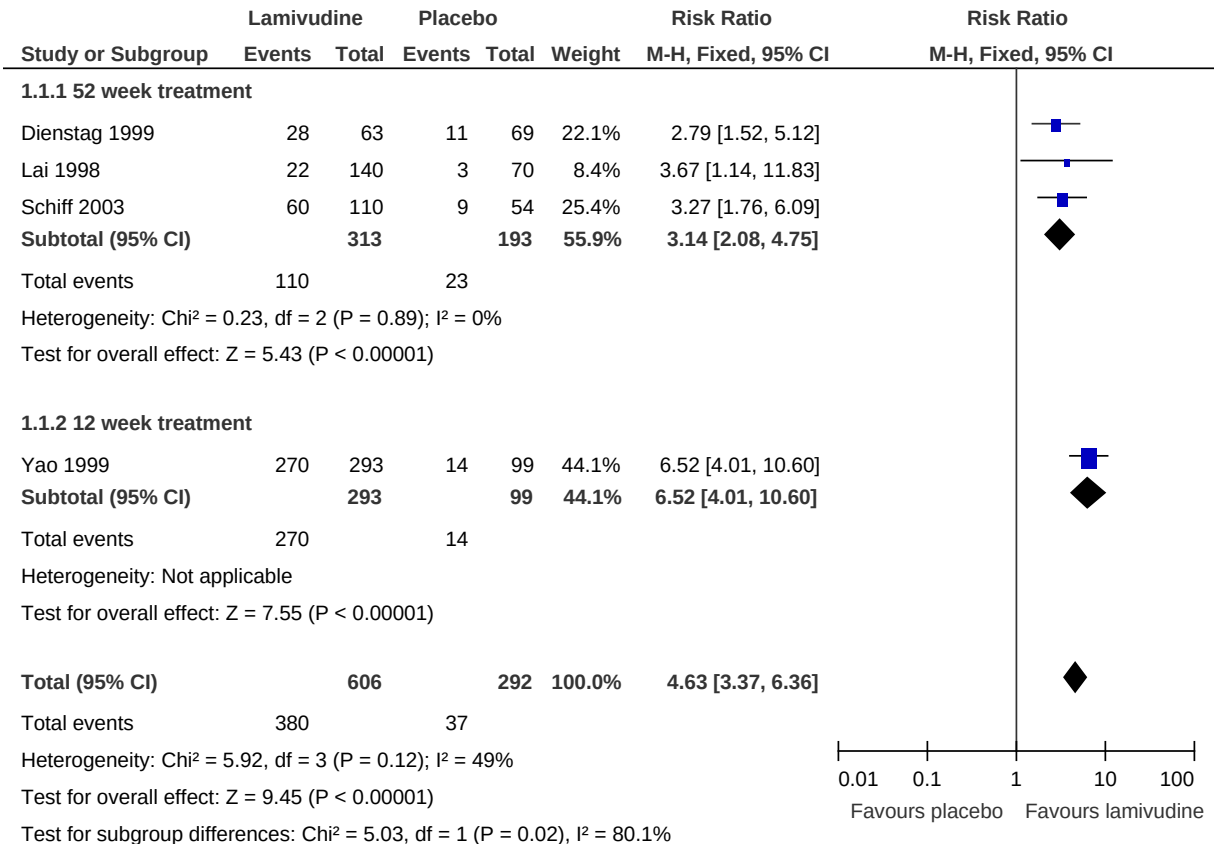


Figure 82: **Loss of serum HBeAg (end of treatment)**

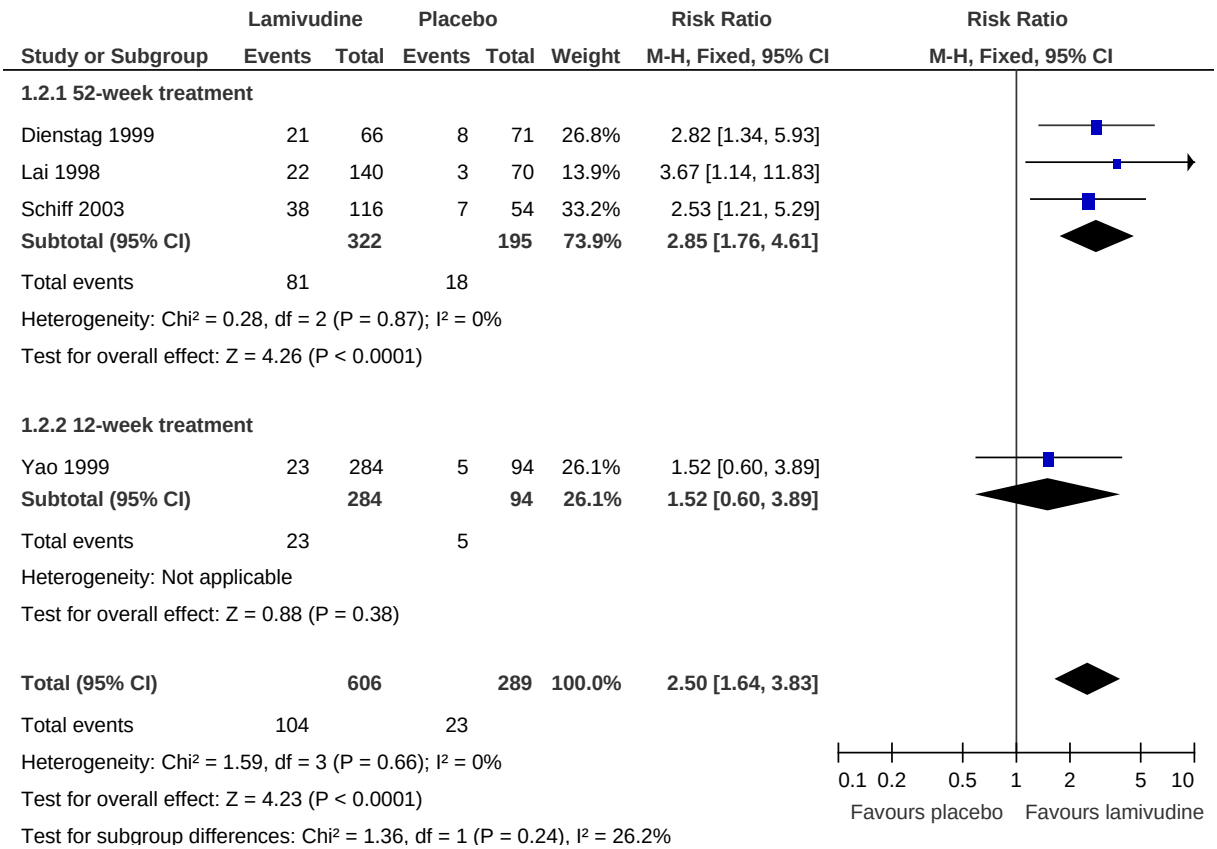


Figure 83: HBeAg seroconversion (end of treatment).

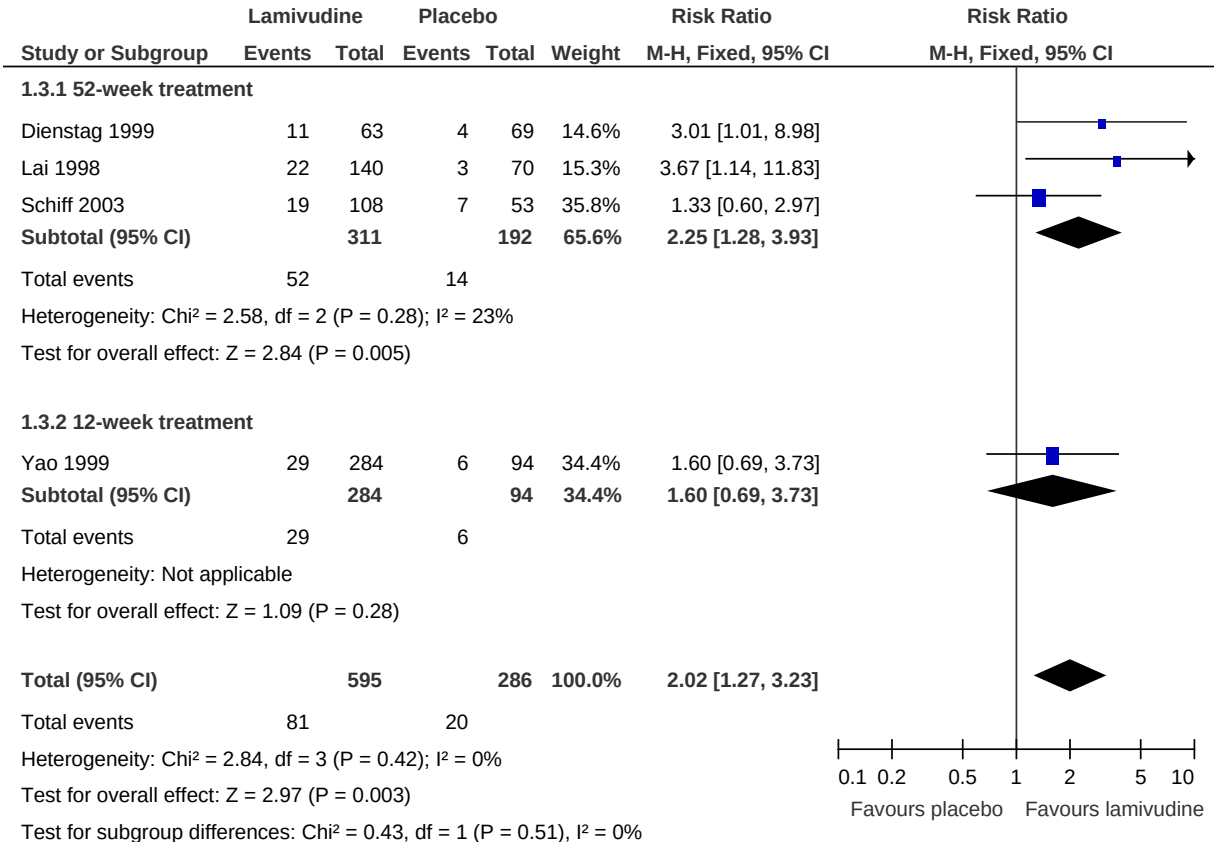


Figure 84: HBsAg seroconversion (end of treatment).

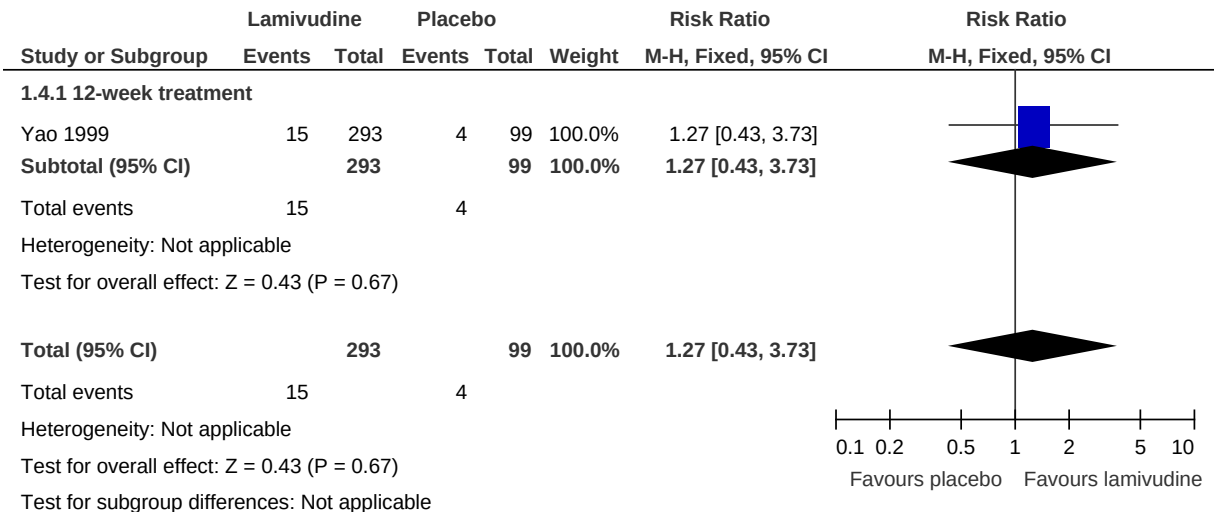


Figure 85: Histologic improvement (end of treatment).

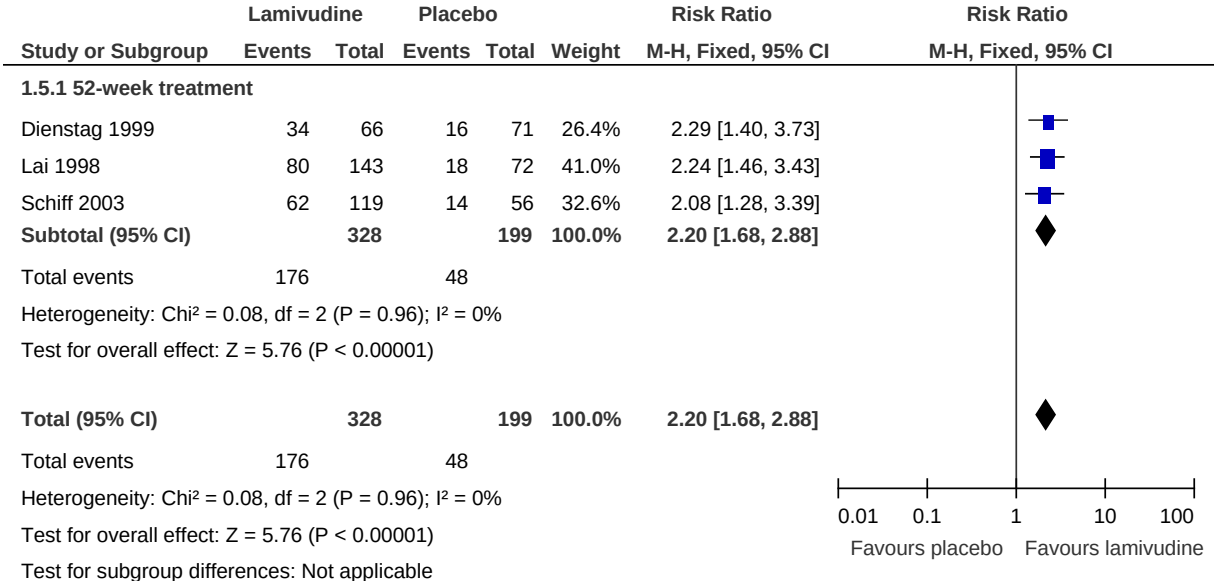


Figure 86: Genotypic mutation (end of treatment)

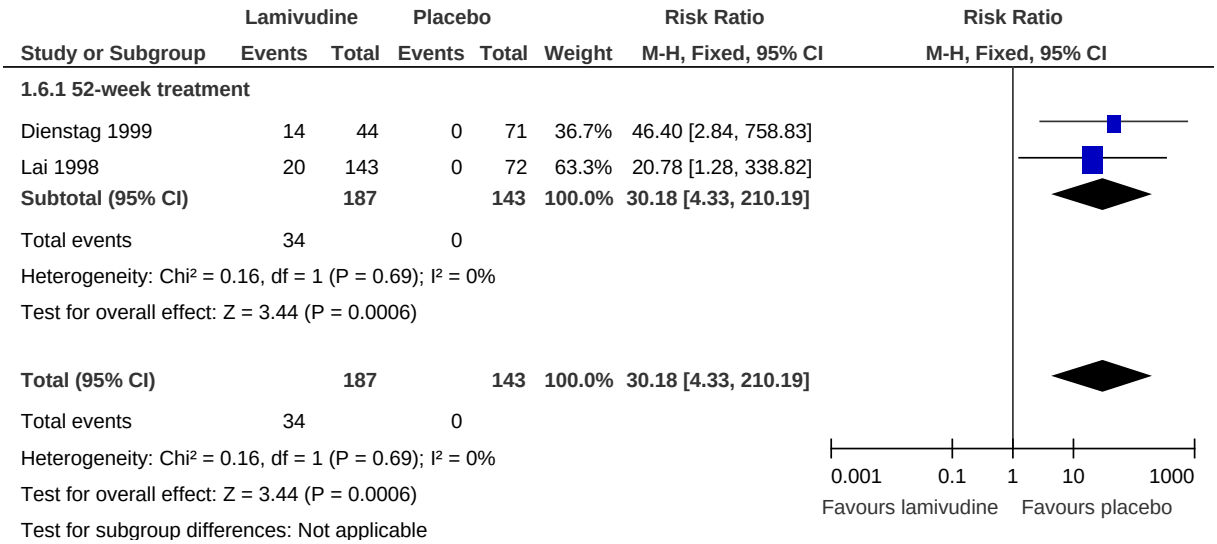


Figure 87: ALT normalization (end of treatment).

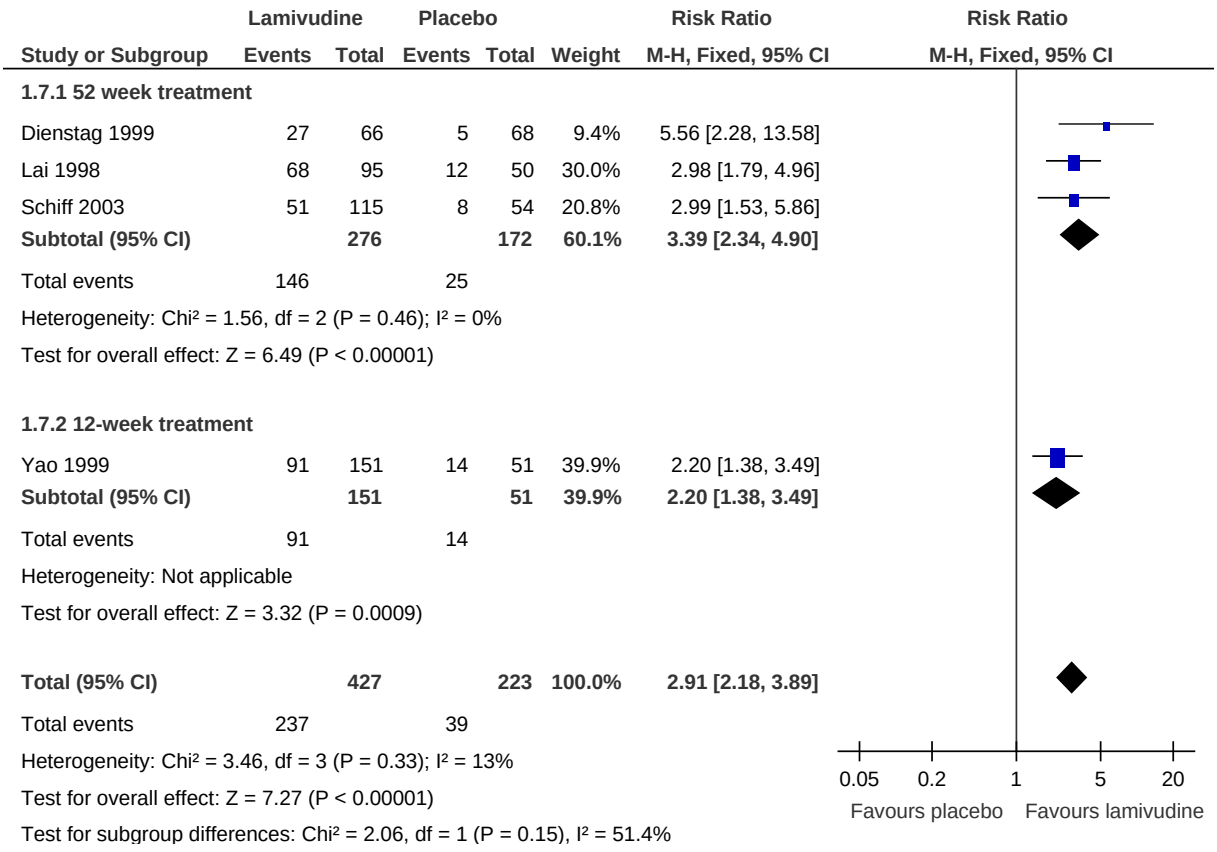


Figure 88: HBeAg seroconversion (16 weeks follow up).

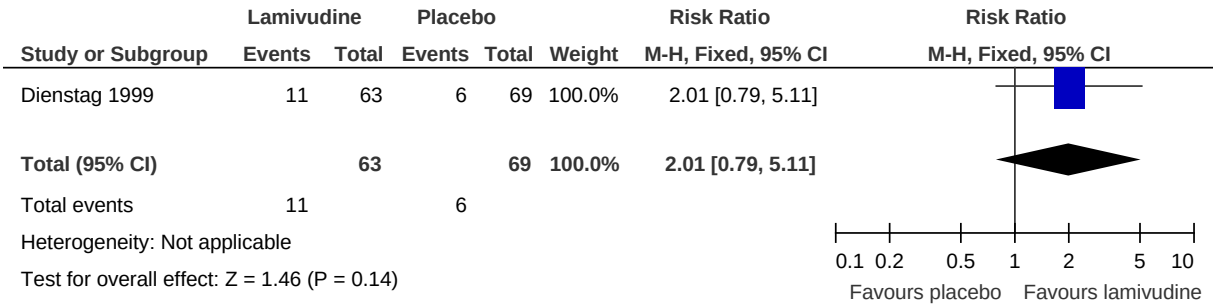


Figure 89: Loss of serum HBeAg (16 weeks follow up).

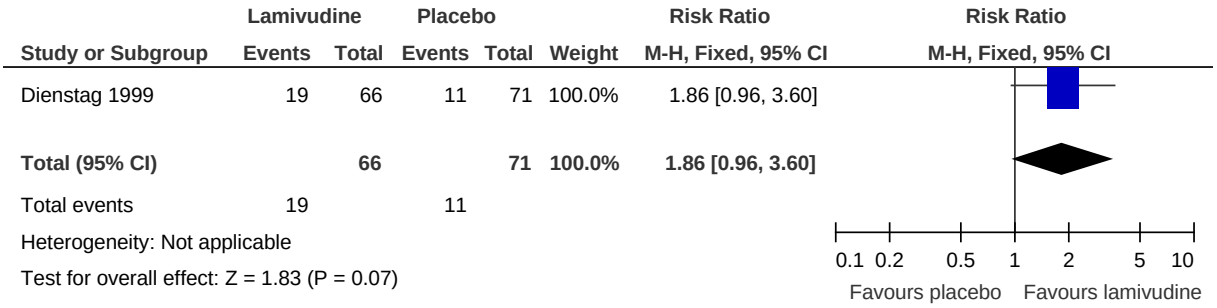


Figure 90: **Loss of serum HBsAg (16 weeks follow up).**

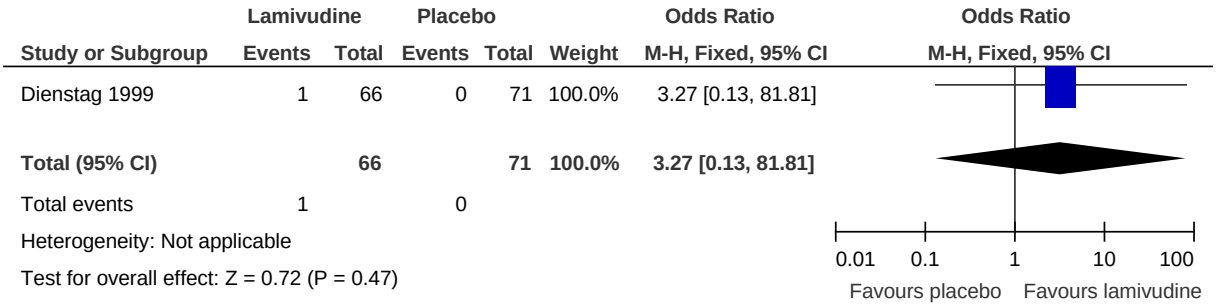
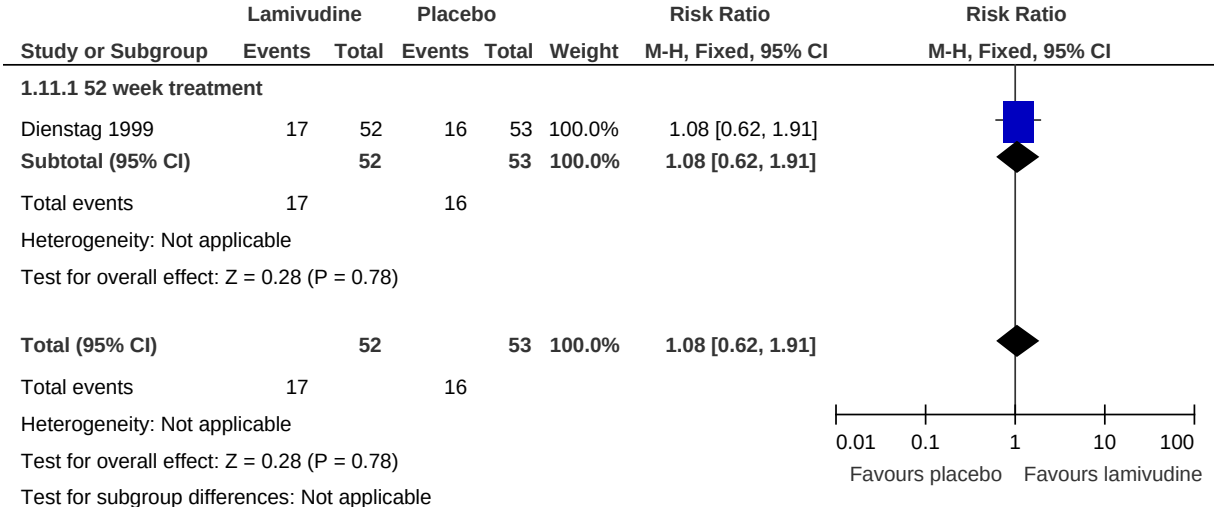
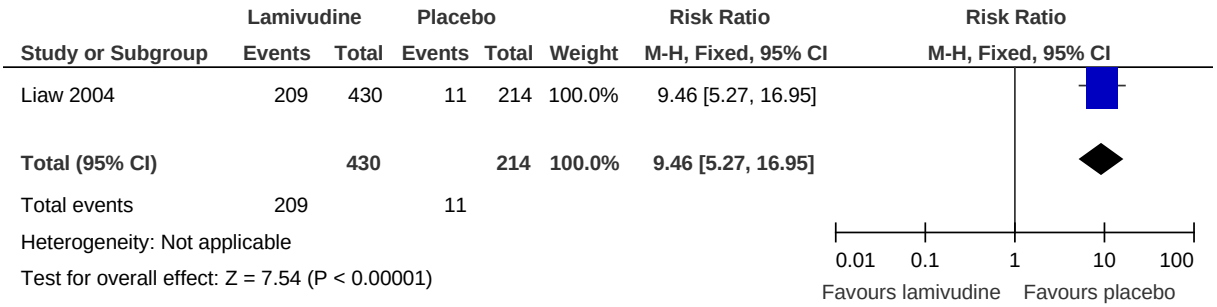


Figure 91: **% of patients with undetectable HBV DNA (<1.6 pg/ml) 16 weeks follow up.**



Lamivudine versus placebo (severe cirrhosis but not decompensation)

Figure 92: **Resistance mutation at end of follow up.**



Comparison of interferon versus lamivudine

Figure 93: **HBeAg seroconversion at week 52.**

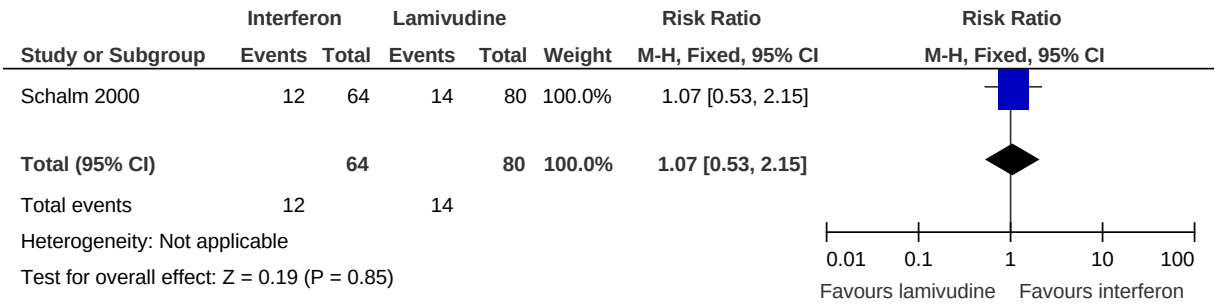


Figure 94: **Histological response at week 52.**

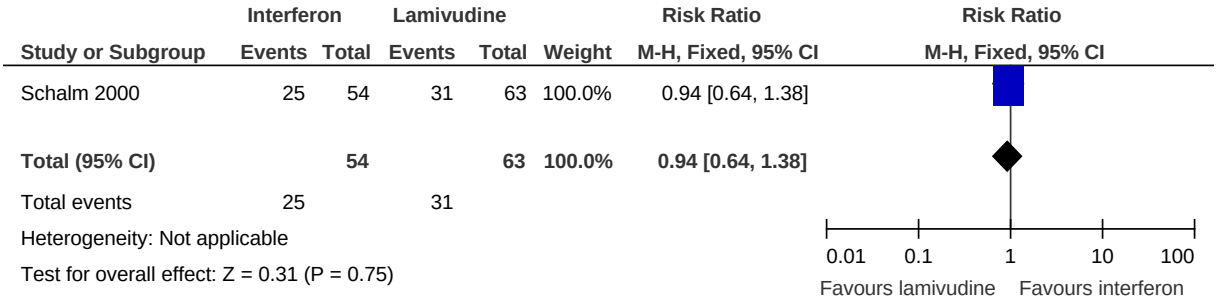


Figure 95: **HBeAg loss at week 52.**

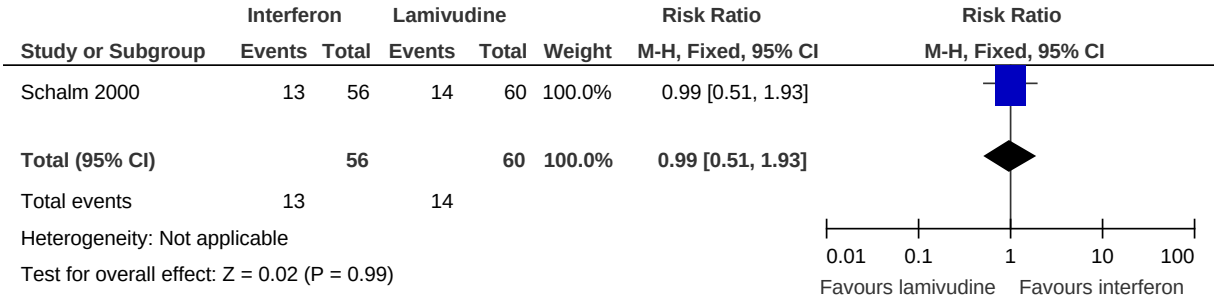


Figure 96: **Undetectable HBV DNA at week 52.**

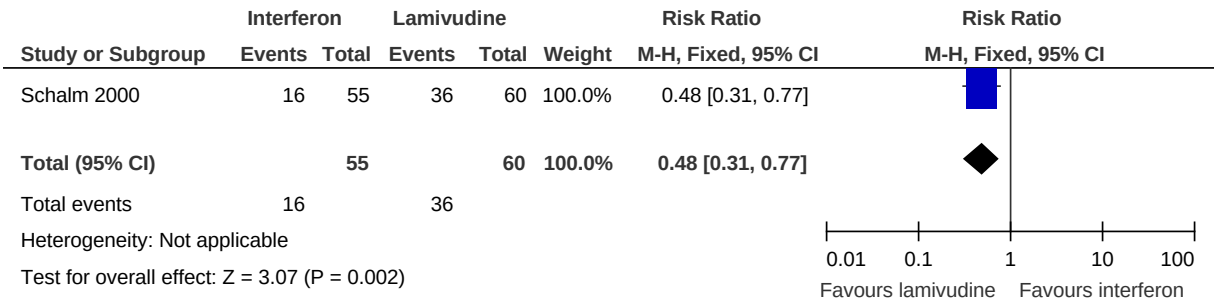


Figure 97: **ALT normalisation at week 52.**

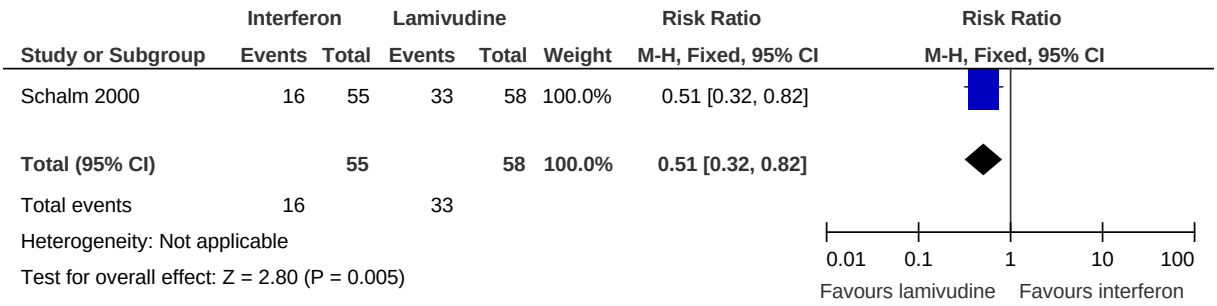


Figure 98: HBeAg seroconversion at week 64

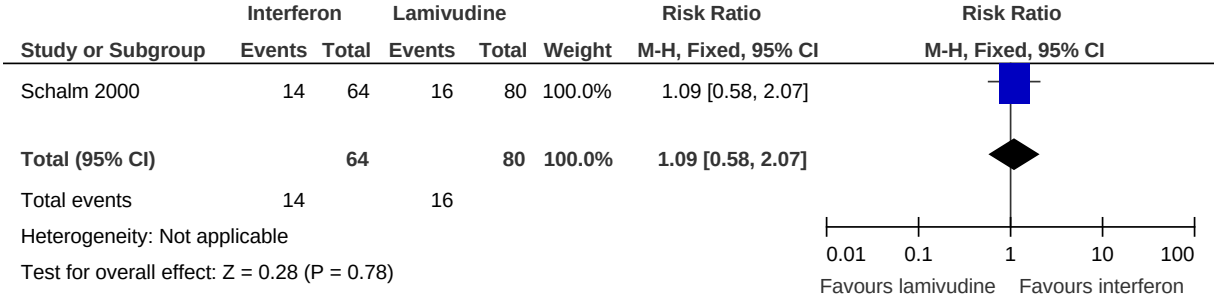


Figure 99: HBeAg loss at week 64.

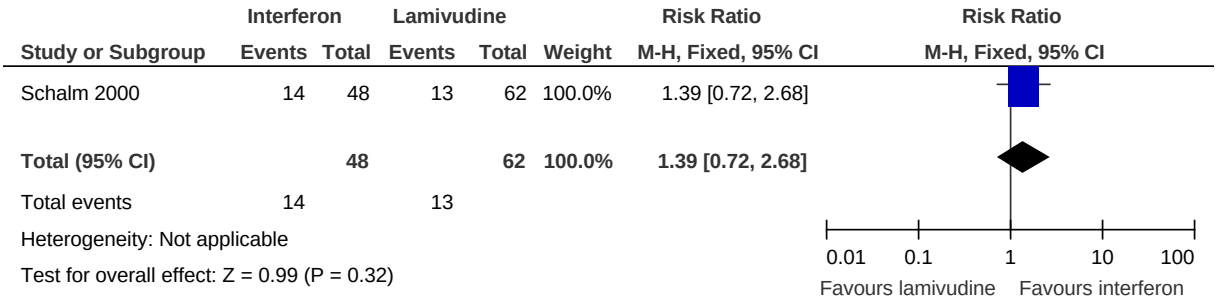


Figure 100: Undetectable HBV DNA at week 64.

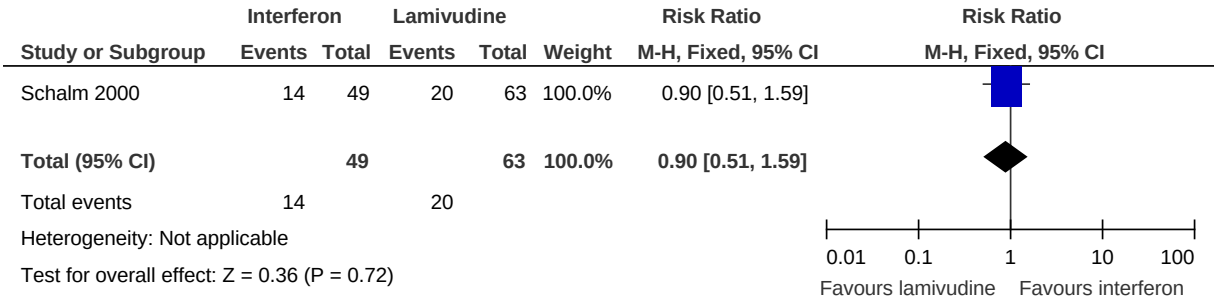
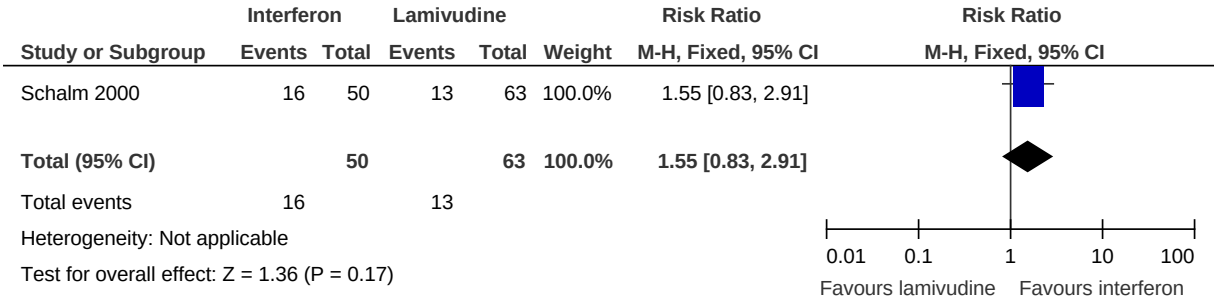


Figure 101: ALT normalisation at week 64



Comparison of pegylated interferon-alpha 2a versus lamivudine (HBeAg positive)

Figure 102: % of people with undetectable HBV DNA (<400 copies/ml) (end of 48 weeks).

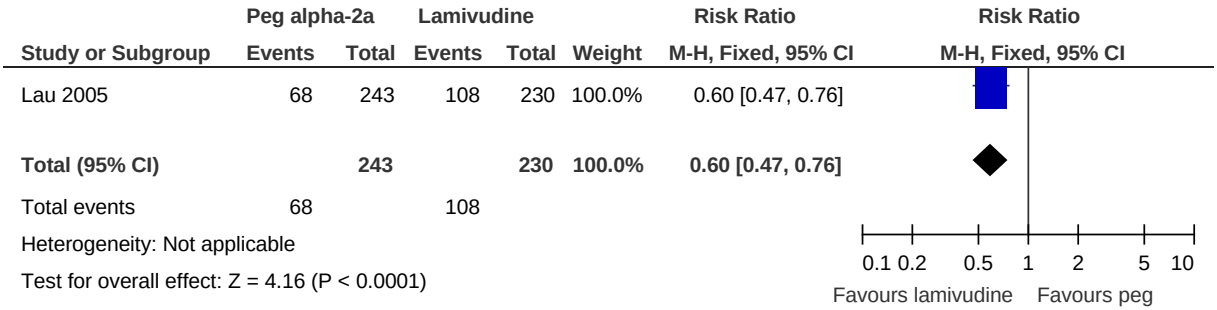


Figure 103: % of people with HBV DNA <100,000 copies/ml (end of 48 weeks).

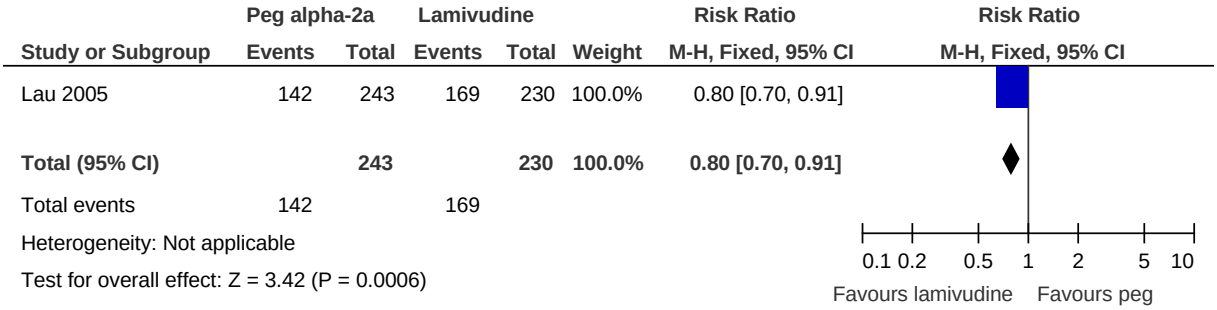


Figure 104: HBeAg seroconversion (48 weeks of treatment).

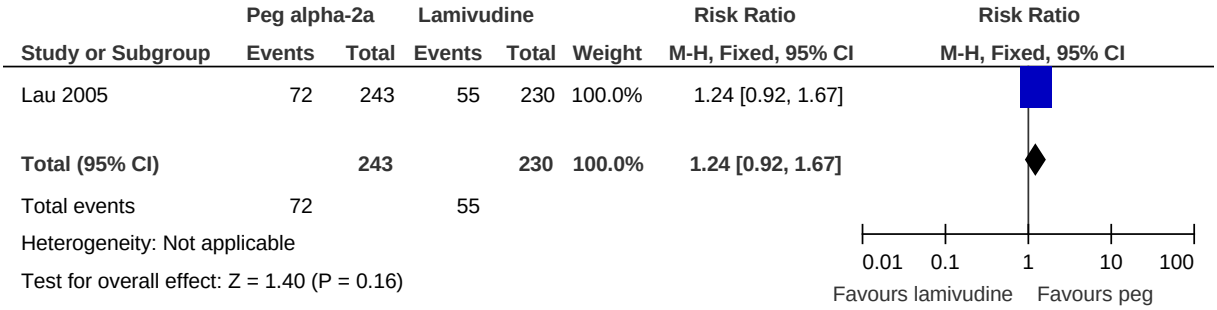


Figure 105: HBeAg loss (48 weeks of treatment).

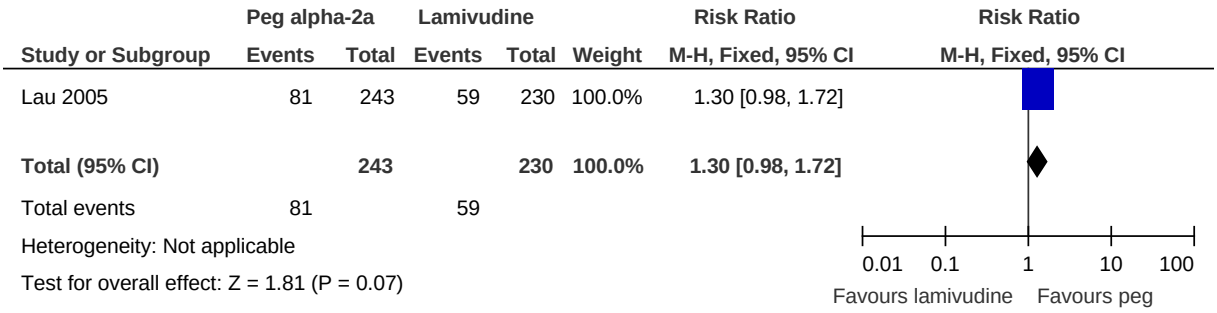


Figure 106: Normalisation of ALT (48 weeks of treatment).

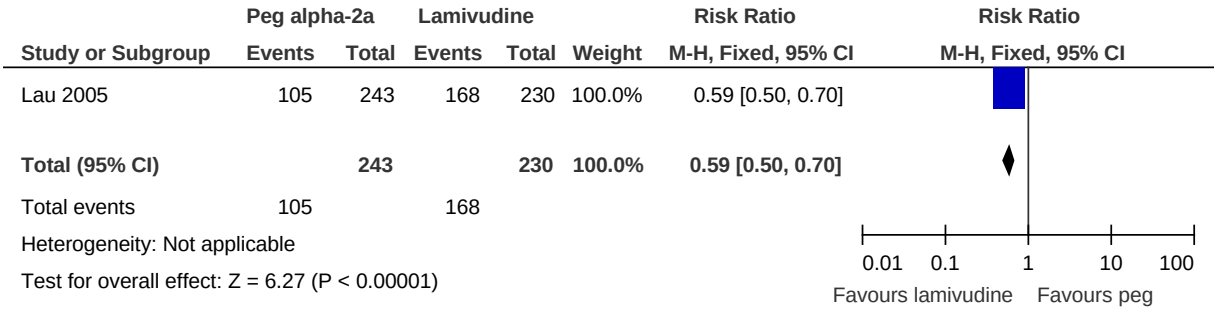


Figure 107: % of people withdrawn due to adverse events.

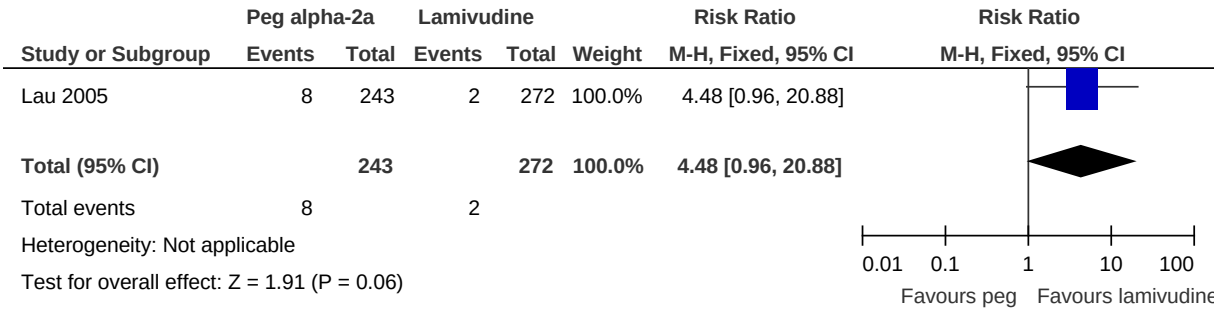


Figure 108: % of people with undetectable HBV DNA (<400 copies/ml) (24 weeks follow up).

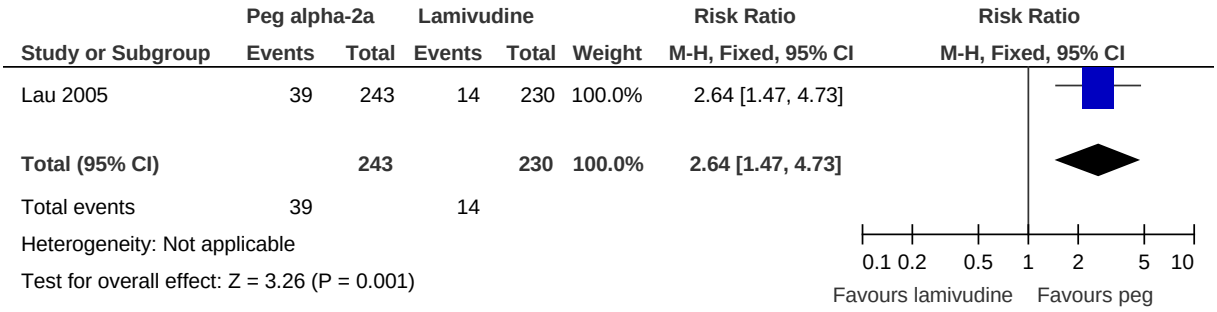


Figure 109: % of people with HBV DNA <100,000 copies/ml (24 weeks follow up).

Study or Subgroup	Peg alpha-2a Events	Total	Lamivudine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lau 2005	86	243	60	230	100.0%	1.36 [1.03, 1.79]
Total (95% CI)		**243**		**230**	**100.0%**	**1.36 [1.03, 1.79]**
Total events	86		60			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.17 (P = 0.03)

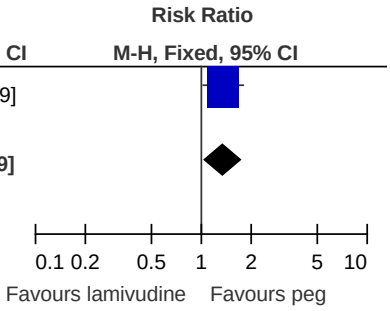


Figure 110: HBeAg seroconversion (24 weeks follow up).

Study or Subgroup	Peg alpha-2a Events	Total	Lamivudine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lau 2005	87	243	52	230	100.0%	1.58 [1.18, 2.12]
Total (95% CI)		**243**		**230**	**100.0%**	**1.58 [1.18, 2.12]**
Total events	87		52			

Heterogeneity: Not applicable

Test for overall effect: Z = 3.08 (P = 0.002)

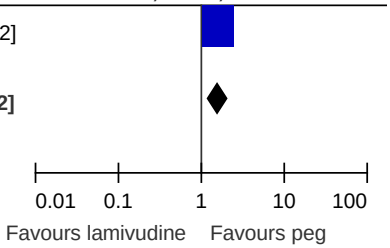


Figure 111: HBeAg loss (24 weeks follow up).

Study or Subgroup	Peg alpha-2a Events	Total	Lamivudine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lau 2005	91	243	57	230	100.0%	1.51 [1.14, 1.99]
Total (95% CI)		**243**		**230**	**100.0%**	**1.51 [1.14, 1.99]**
Total events	91		57			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.91 (P = 0.004)

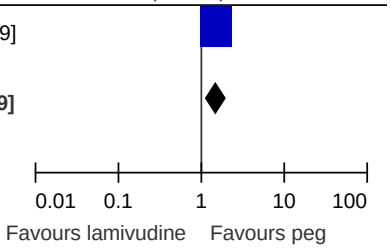
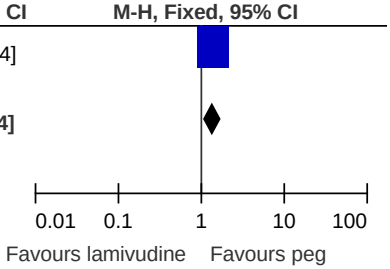


Figure 112: Normalisation of ALT (24 weeks follow up).

Study or Subgroup	Peg alpha-2a Events	Total	Lamivudine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lau 2005	111	243	76	230	100.0%	1.38 [1.10, 1.74]
Total (95% CI)		**243**		**230**	**100.0%**	**1.38 [1.10, 1.74]**
Total events	111		76			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.77 (P = 0.006)



Comparison of Lamivudine plus adefovir versus lamivudine

Figure 113: HBV DNA < 10000 copies/mL at 52 weeks

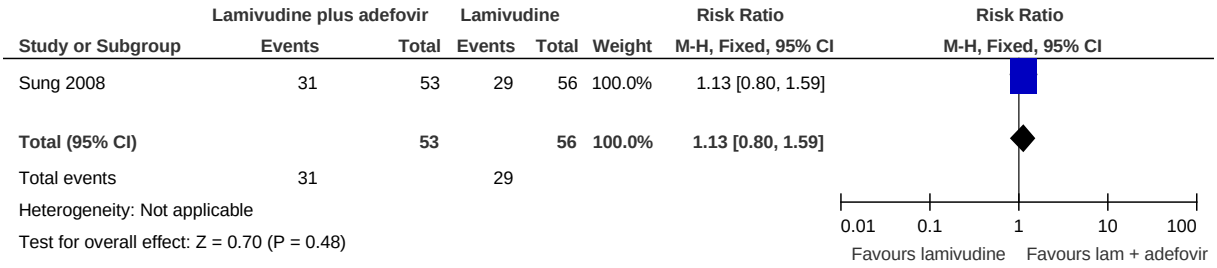


Figure 114: Undetectable HBV DNA < 200 copies/mL at 52 weeks.

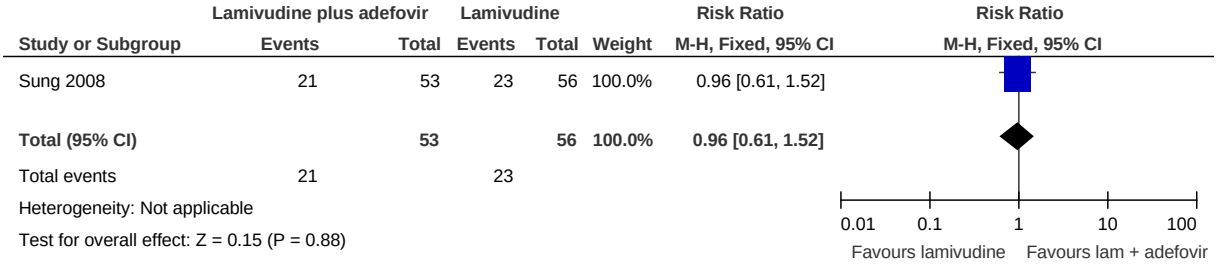


Figure 115: ALT normalisation at 52 weeks.

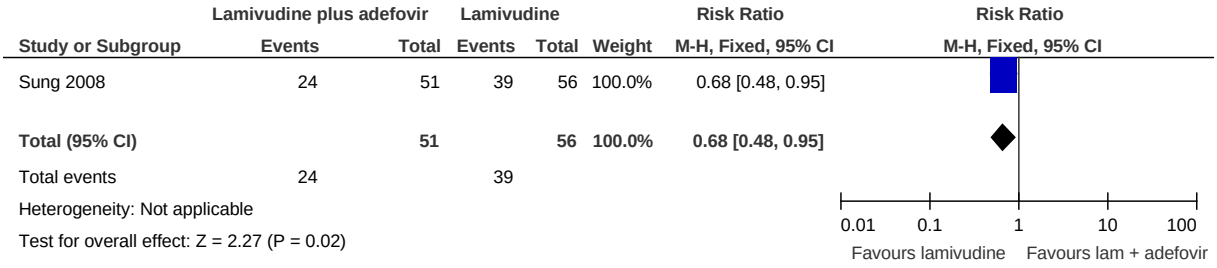


Figure 116: HBeAg loss at 52 weeks.

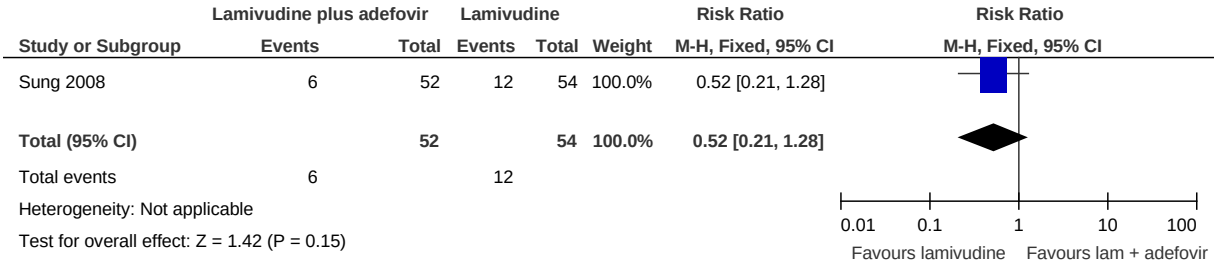


Figure 117: HBeAg seroconversion at 52 weeks.

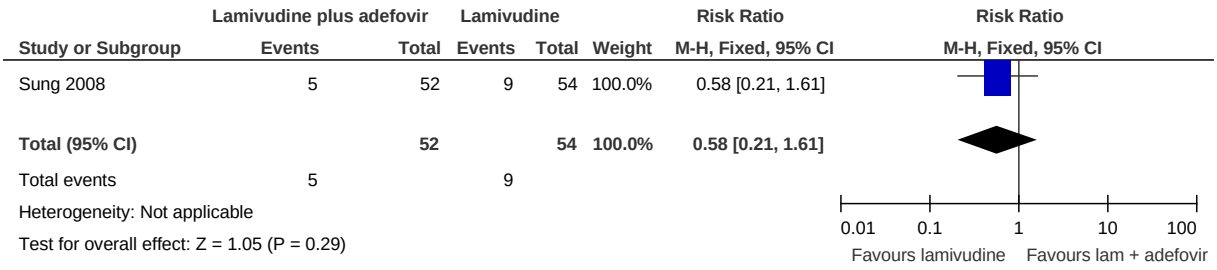
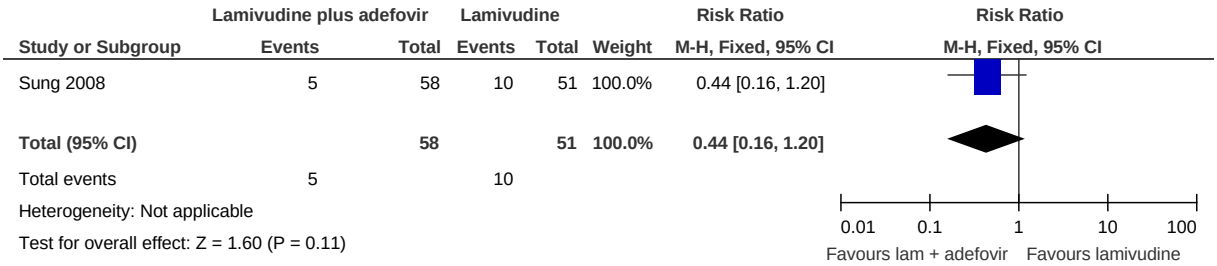


Figure 118: Resistance mutation at 52 weeks.



Comparison of telbivudine versus adefovir

Figure 119: Log reduction in HBV DNA (assessed at the end of treatment)

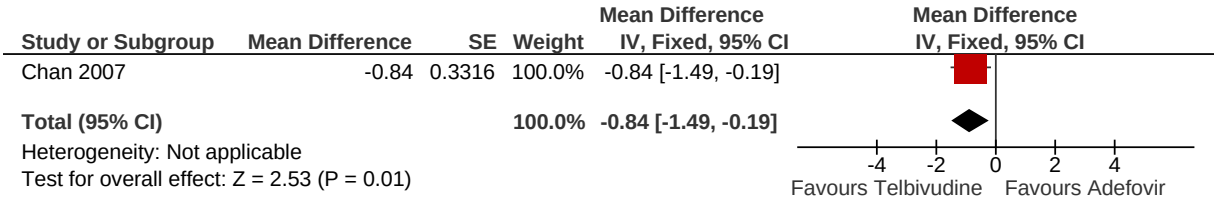


Figure 120: % of people with undetectable HBV DNA (<300 copies/mL)

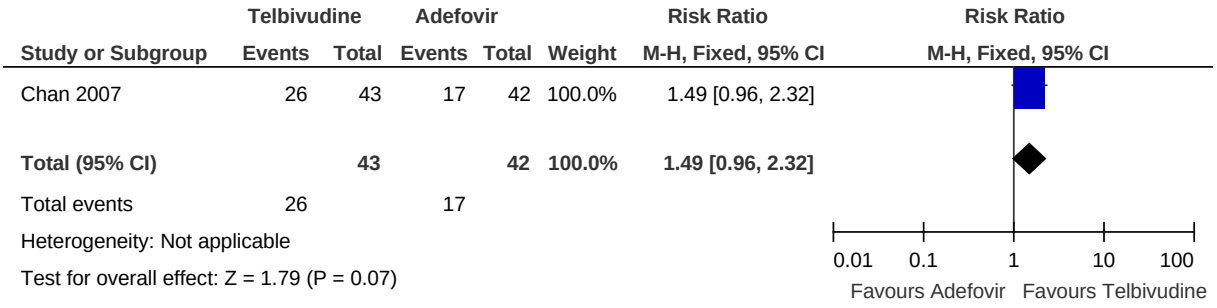


Figure 121: % of people with Clearance of HBeAg (assessed at the end of treatment)

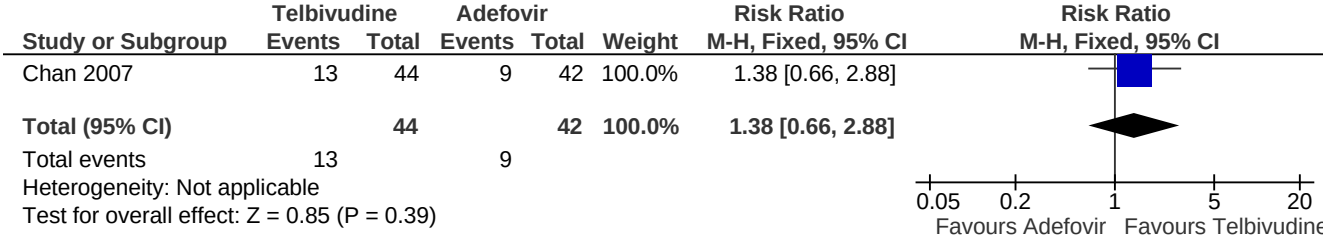


Figure 122: % of people with Seroconversion of HBeAg (assessed at the end of treatment)

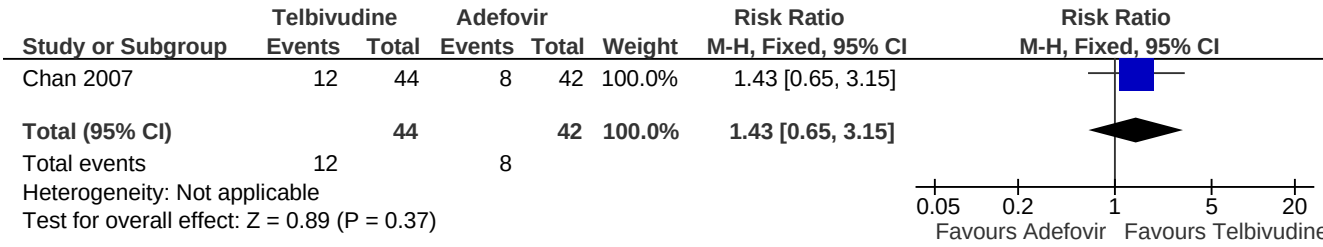
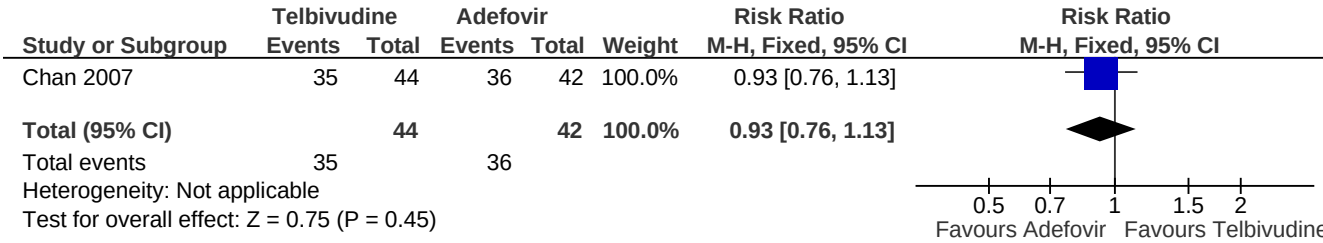


Figure 123: Normalisation of serum ALT (assessed at the end of treatment)



Comparison of telbivudine versus entecavir (HBeAg positive people)

Figure 124: Log reduction in HBV DNA (assessed at the end of treatment)

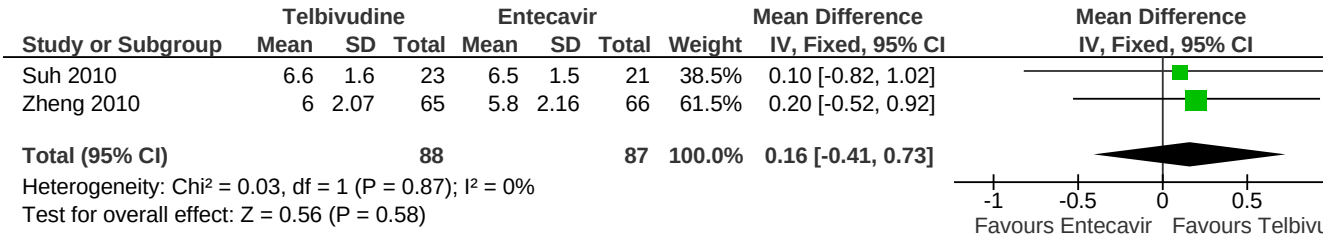


Figure 125: % of people with continuing undetectable HBV DNA (≥500 copies/mL) (assessed at the end of treatment)

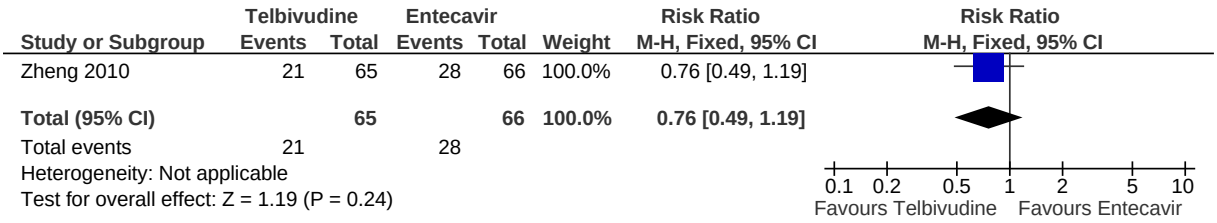


Figure 126: % of people with Clearance of HBeAg (assessed at the end of treatment)

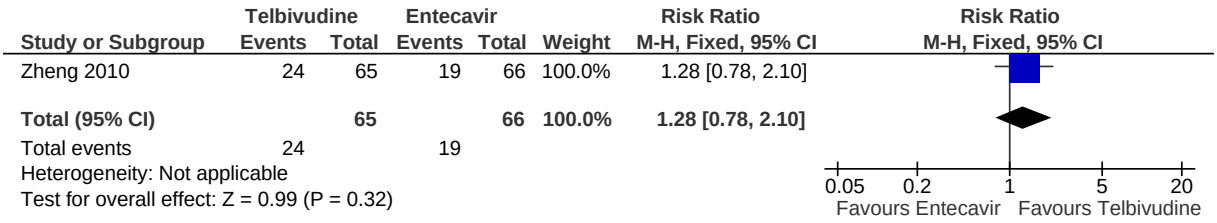


Figure 127: % of people with Seroconversion of HBeAg (assessed at the end of treatment)

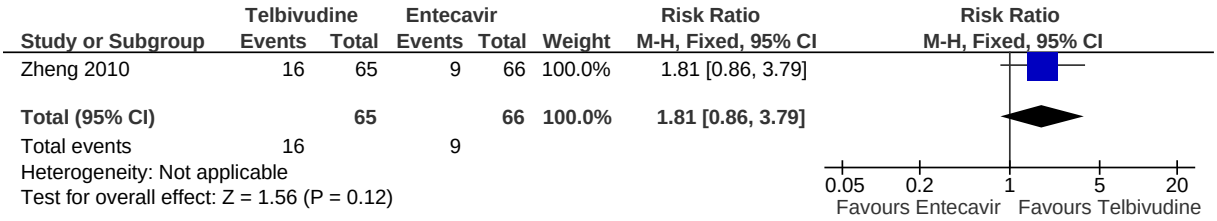
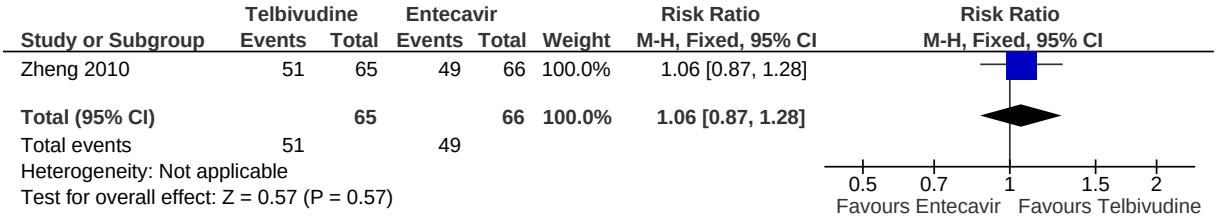


Figure 128: Normalisation of serum ALT (≤1 x ULN) (end of treatment)



Comparison of telbivudine versus lamivudine (HBeAg positive people)

Figure 129: Log reduction in HBV DNA (week 52)

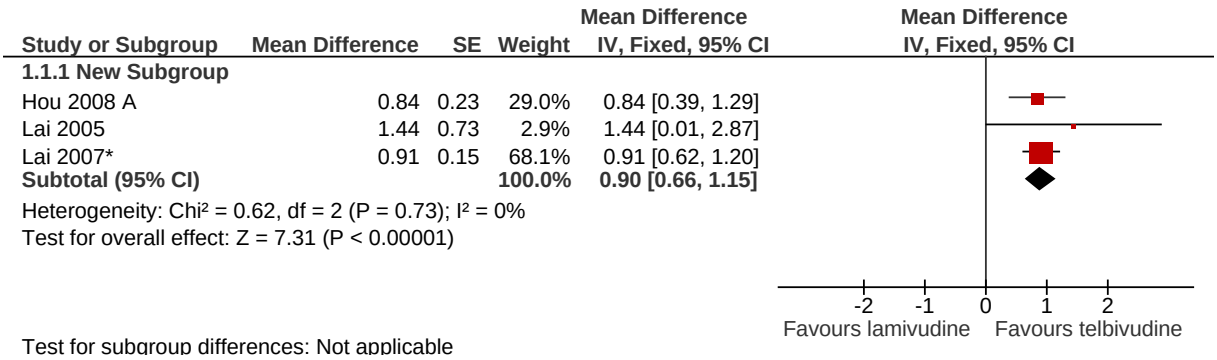


Figure 130: % of people with continuing undetectable HBV DNA

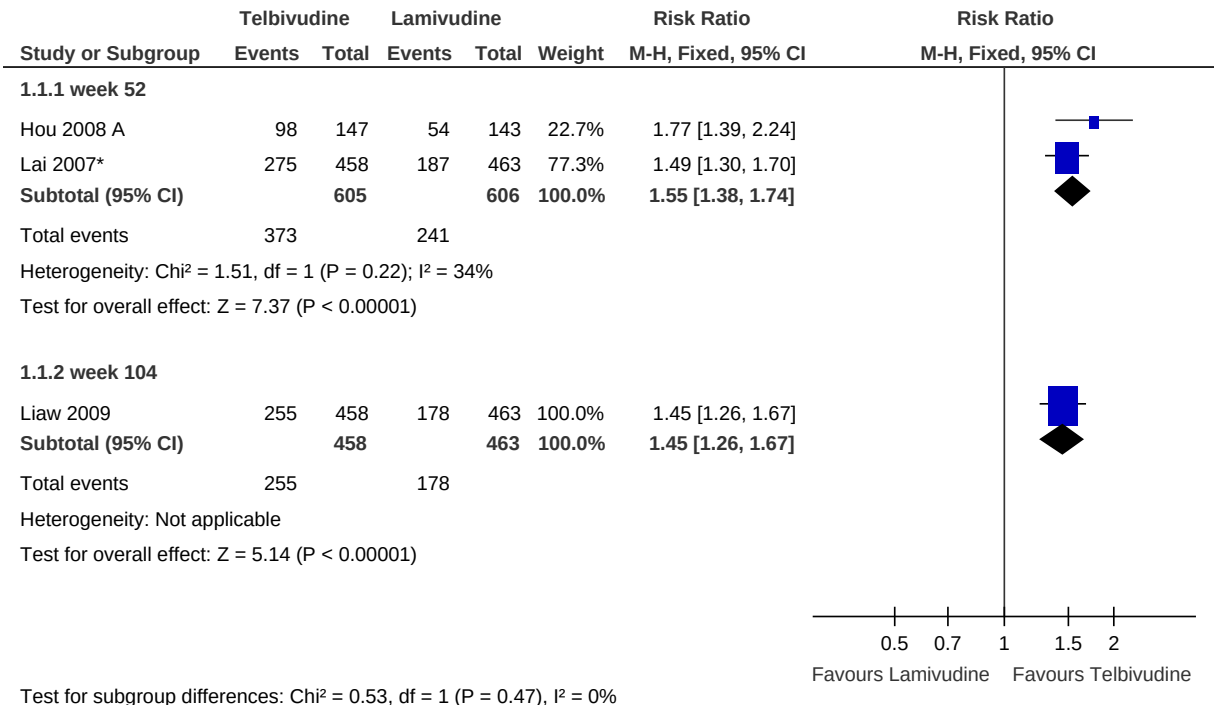


Figure 131: % of people with Clearance of HBeAg (assessed at the end of treatment)

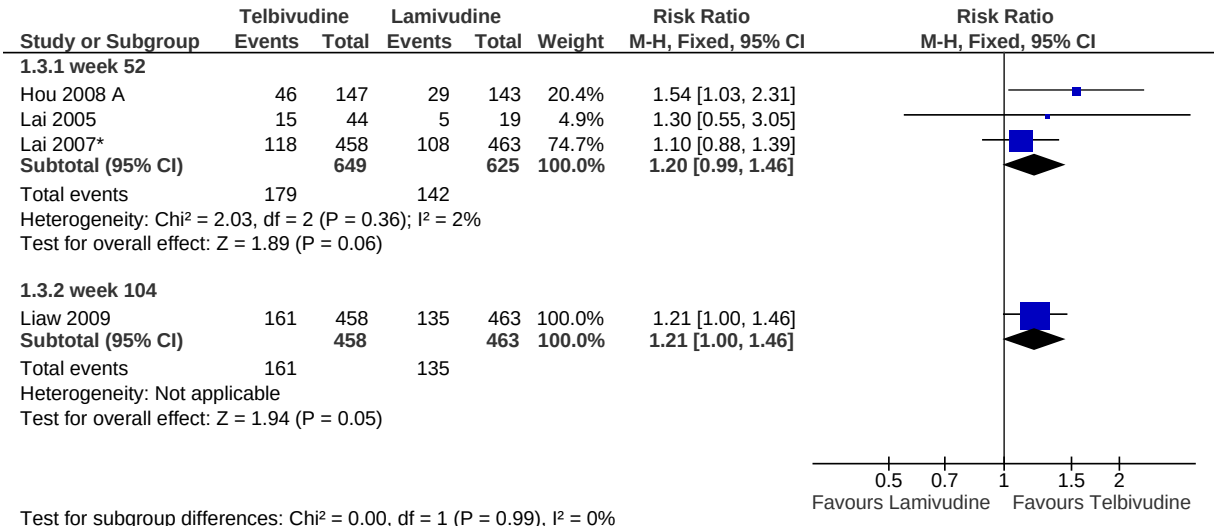


Figure 132: % of people with Seroconversion of HBeAg (assessed at the end of treatment)

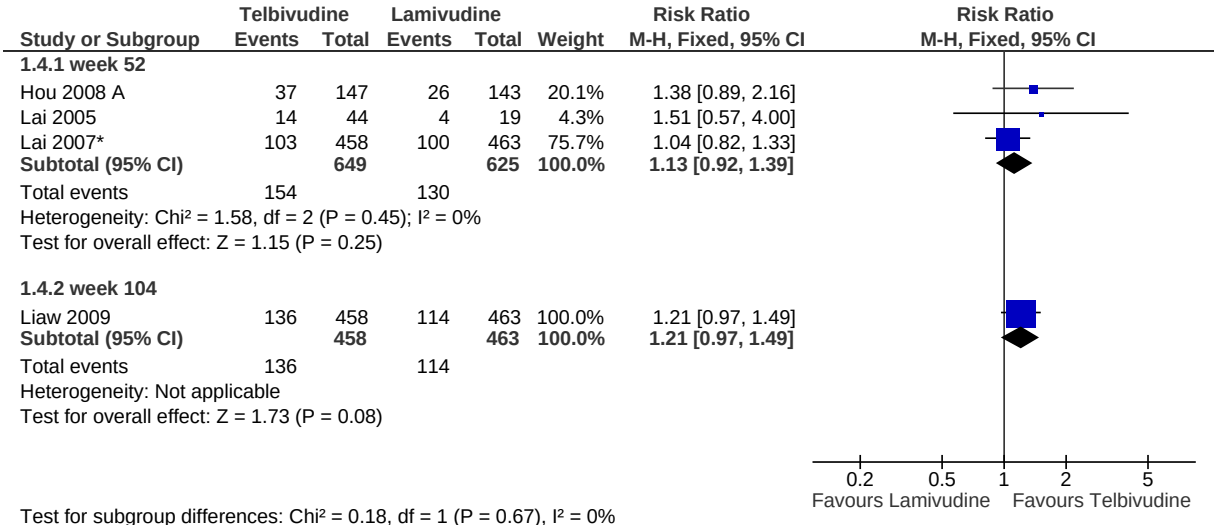


Figure 133: % of people with Clearance of HBsAg

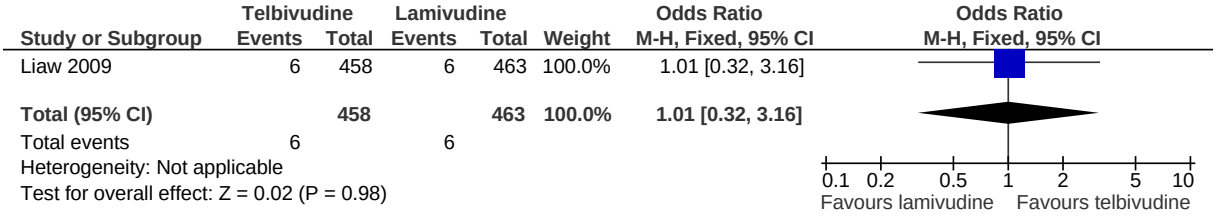


Figure 134: % of people with Seroconversion of HBsAg

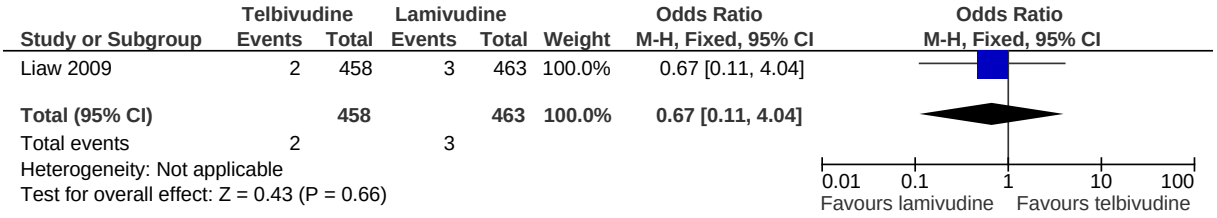


Figure 135: Normalisation of serum ALT (end of treatment)

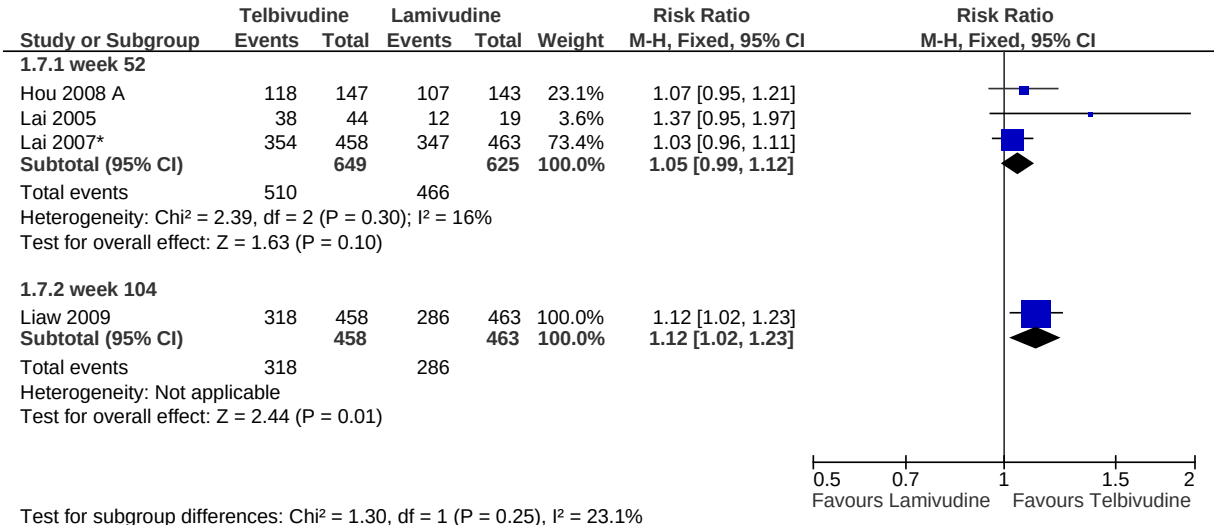


Figure 136: Incidence of viral resistance (viral breakthrough accompanied by genotypic mutation)

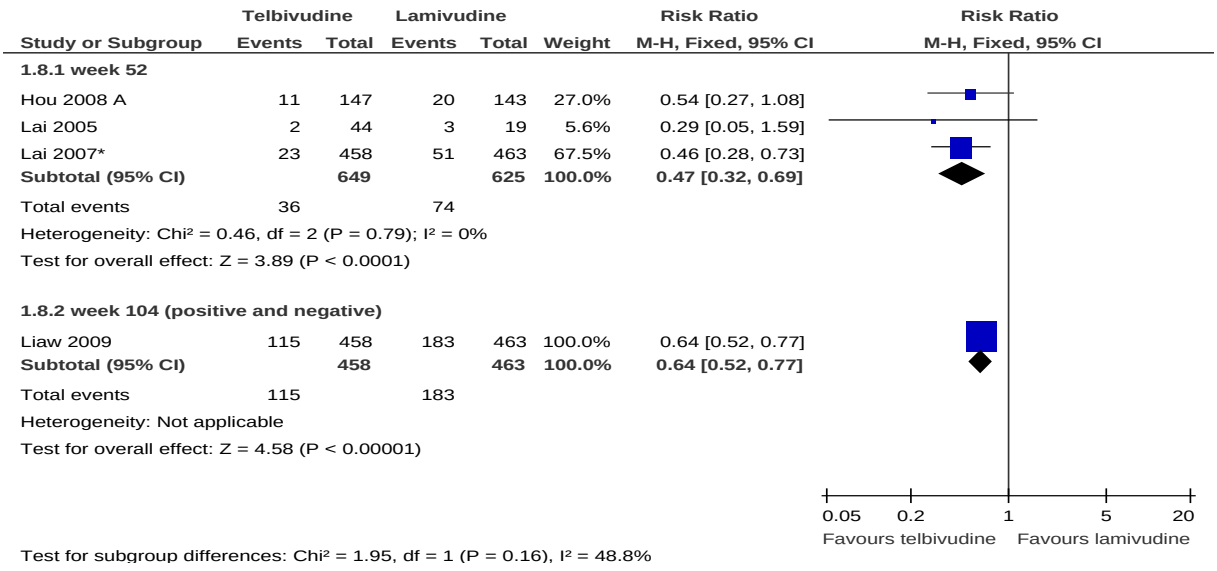


Figure 137: Incidence of resistance – viral breakthrough

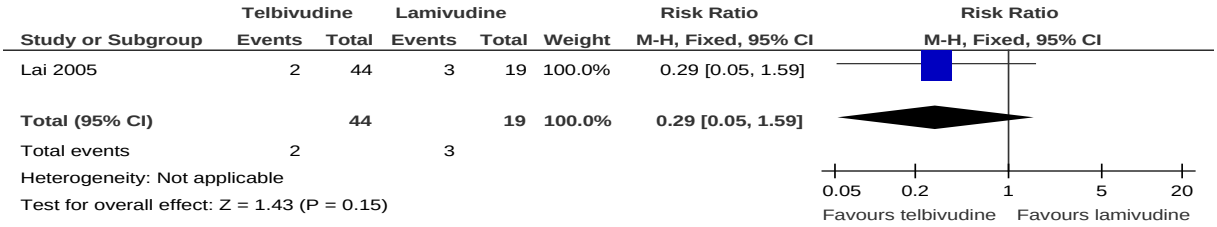
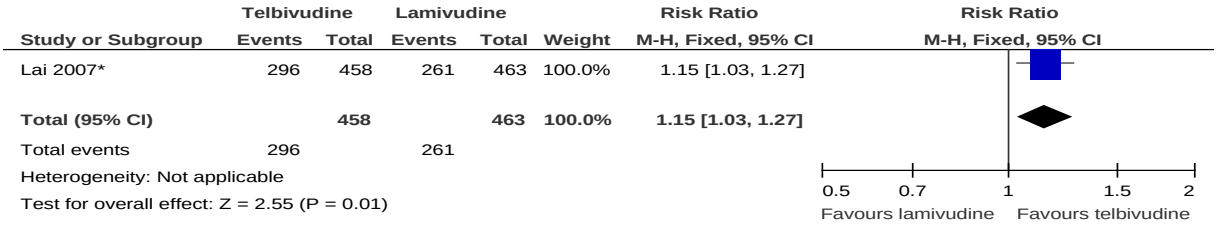


Figure 138: % of people with Histologic improvement



Comparison of tenofovir versus adefovir (HBeAg positive)

Figure 139: Reduction of HBV DNA

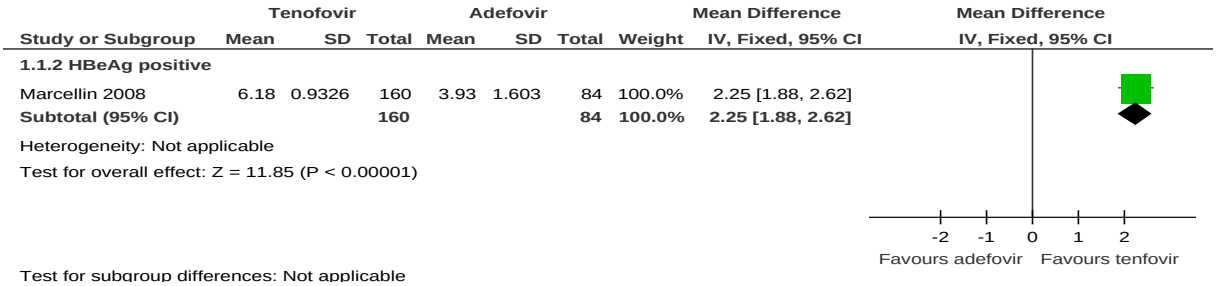


Figure 140: % of people with HBV DNA <400 copies/mL

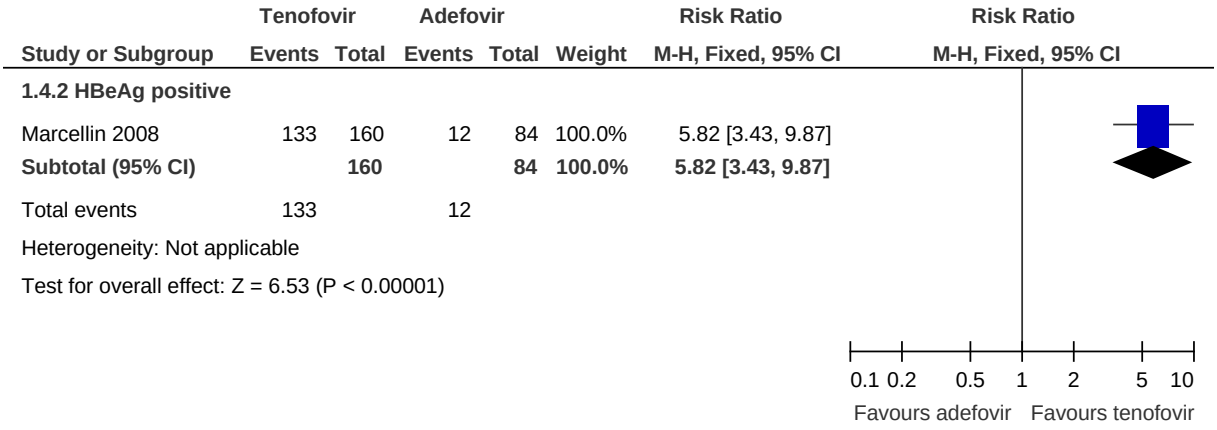


Figure 141: % of people with HBeAg seroconversion

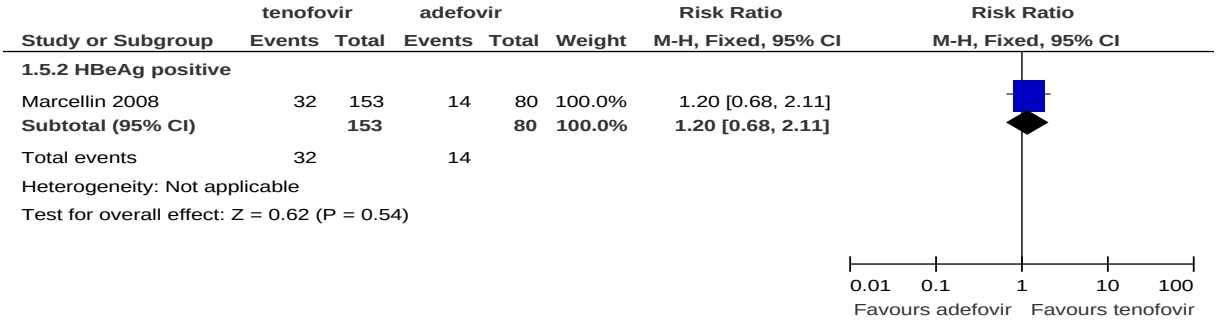


Figure 142: % of people with ALT normalisation

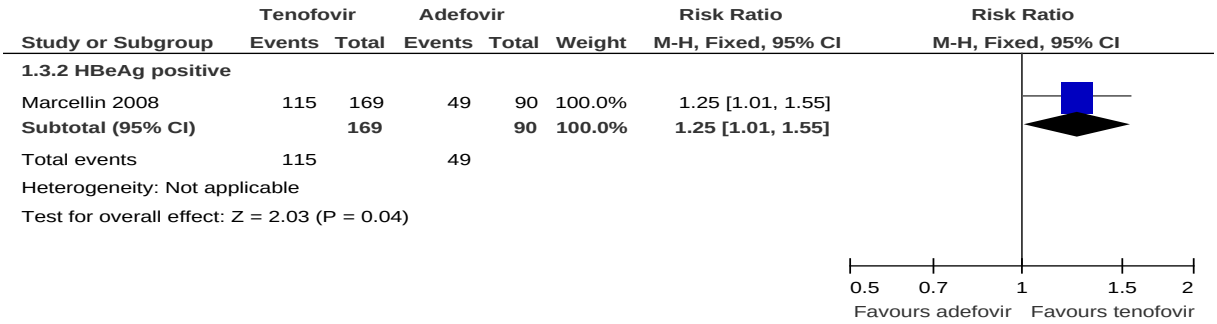


Figure 143: % of people with HBsAg loss

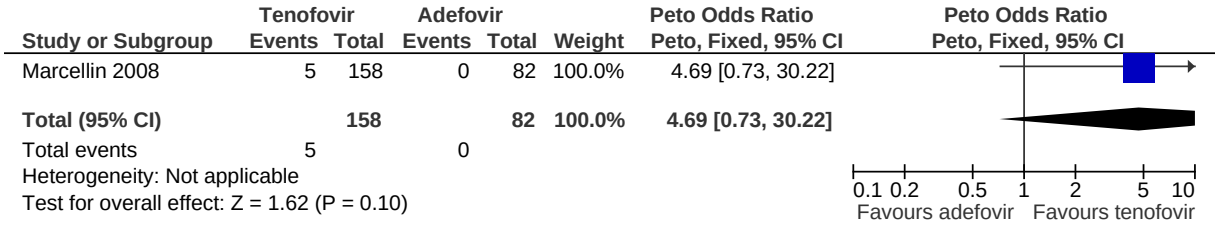
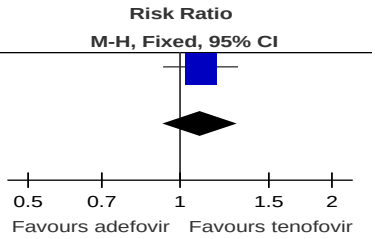


Figure 144: % of people with Histologic improvement

Study or Subgroup	Tenofovir Events	Total	Adefovir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marcellin 2008	131	176	61	90	100.0%	1.10 [0.93, 1.30]
Total (95% CI)		**176**		**90**	**100.0%**	**1.10 [0.93, 1.30]**
Total events	131		61			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



Comparison of entecavir versus lamivudine

Figure 145: Log reduction of HBV DNA (end of treatment).

Study or Subgroup	Entecavir Mean	SD	Total	Lamivudine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chang 2006	6.9	2	340	5.4	2.6	321	32.4%	1.50 [1.14, 1.86]
Shindo 2009A	5.16	0.74	32	4.29	1.03	33	21.6%	0.87 [0.43, 1.31]
Yao 2007	6	1.08	225	4.3	1.992	221	46.0%	1.70 [1.40, 2.00]
Total (95% CI)			**597**			**575**	**100.0%**	**1.46 [1.25, 1.66]**

Heterogeneity: Chi² = 9.60, df = 2 (P = 0.008); I² = 79%
Test for overall effect: Z = 14.11 (P < 0.00001)

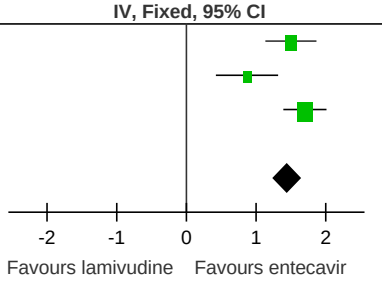


Figure... % with undetectable HBV DNA (<300 copies/mL) (end of treatment week 48).

Study or Subgroup	Entecavir Events	Total	Lamivudine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chang 2006	236	340	129	321	59.1%	1.73 [1.49, 2.01]
Ren 2007	15	21	8	21	3.6%	1.88 [1.02, 3.45]
Yao 2007	166	225	83	221	37.3%	1.96 [1.63, 2.37]
Total (95% CI)		**586**		**563**	**100.0%**	**1.82 [1.62, 2.04]**
Total events	417		220			

Heterogeneity: Chi² = 1.11, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 10.19 (P < 0.00001)

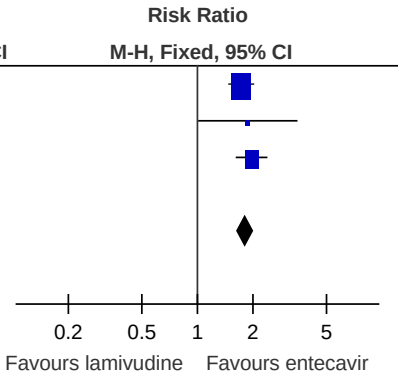


Figure 146: **% with undetectable HBV DNA (<0.7MEq/mL) (end of treatment week 48).**

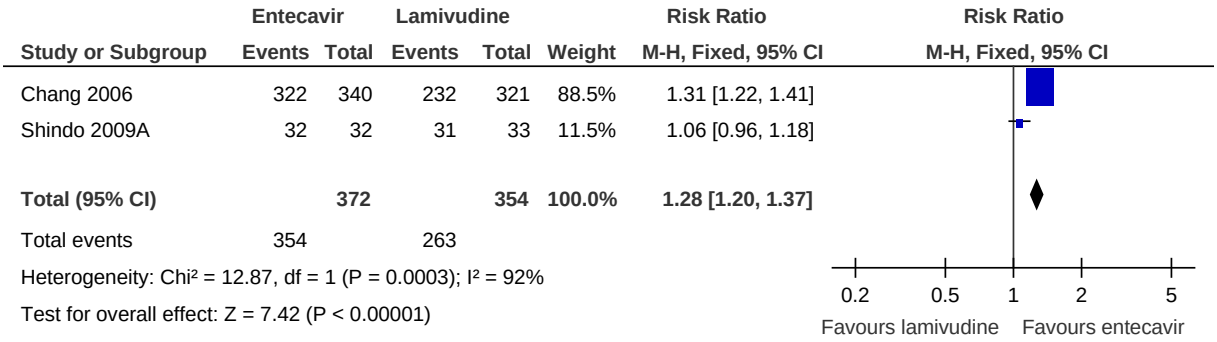


Figure 147: **% with HBeAg loss (end of treatment week 48).**

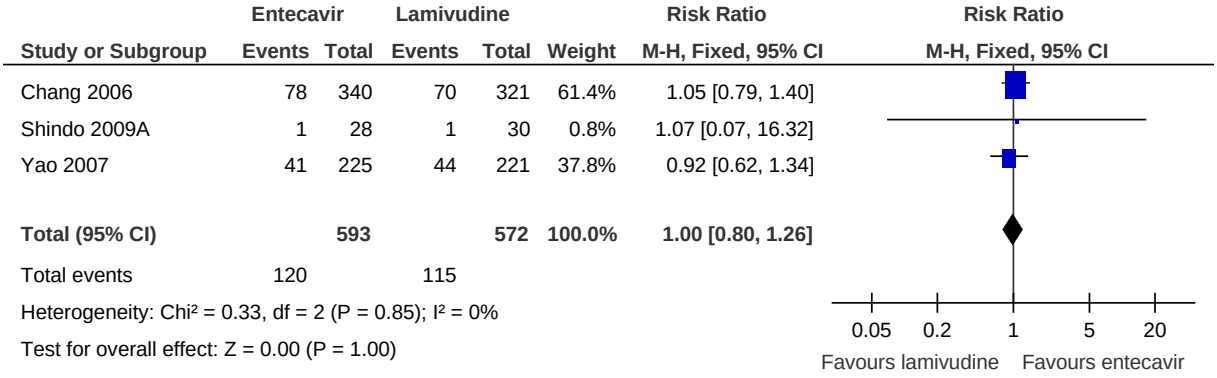


Figure 148: **with HBeAg seroconversion (end of treatment week 48).**

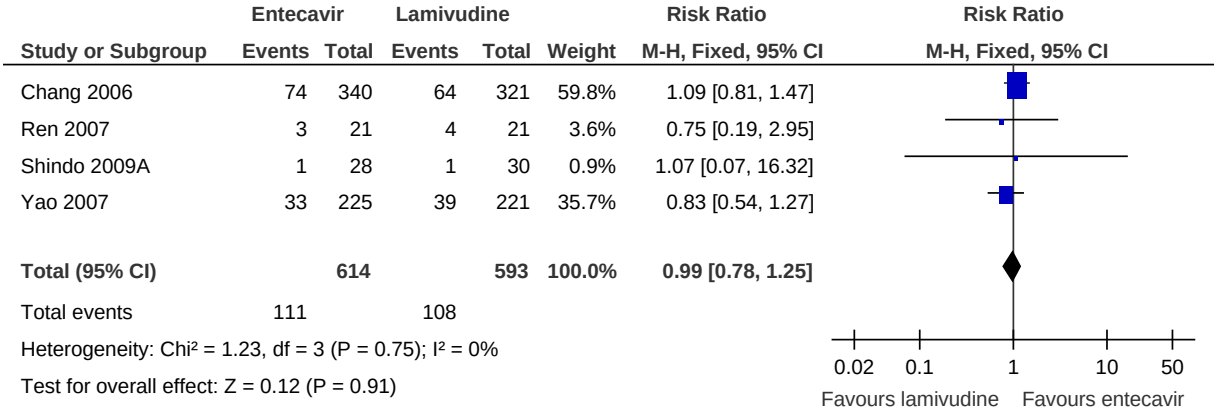


Figure 149: **% with ALT normalisation (end of treatment week 48).**

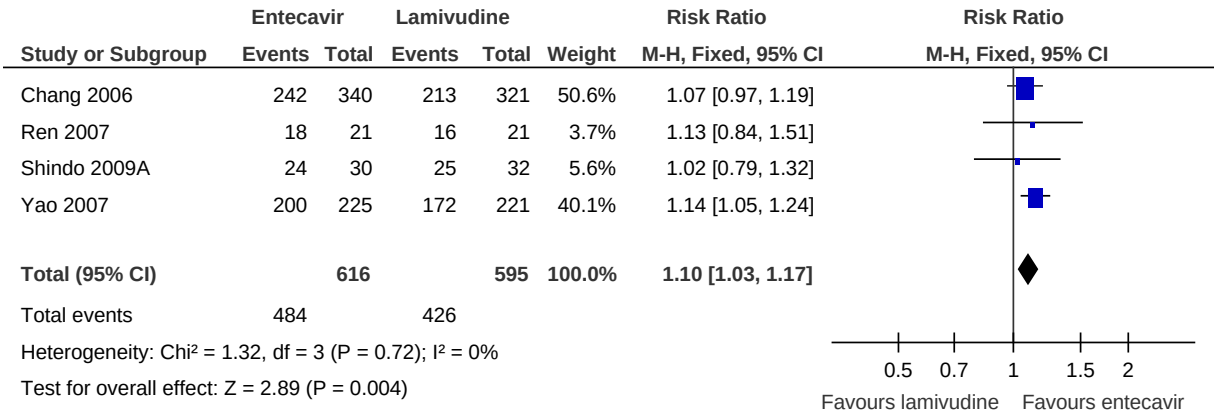


Figure 150: % with HBsAg loss (end of treatment week 48).

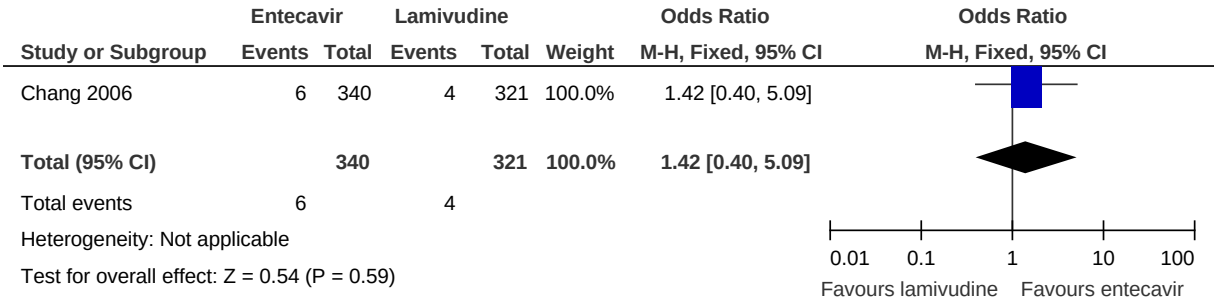


Figure 151: % discontinuation due to adverse events (end of treatment week 48).

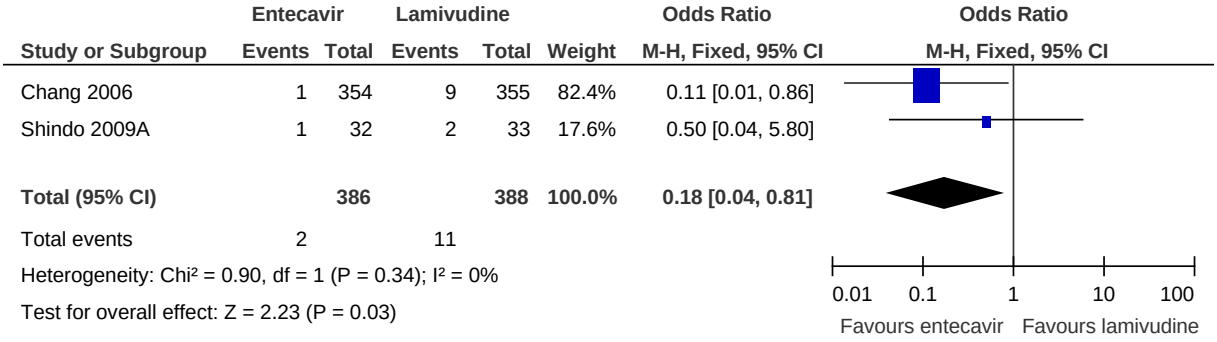


Figure 152: Histologic improvement.

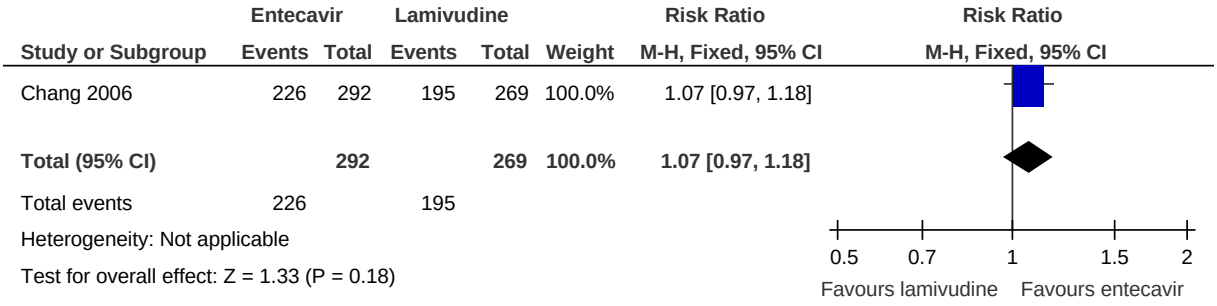
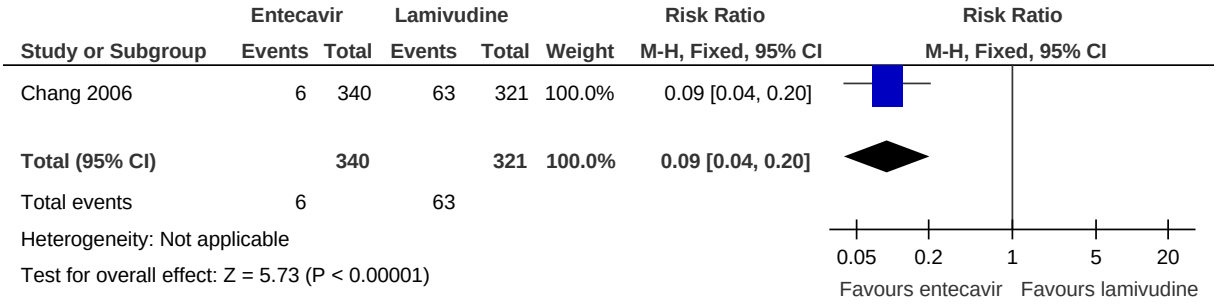


Figure 153: Viral breakthrough.



Comparison of entecavir versus adefovir

The results are reported in a systematic review of six studies by Zhao et al 2011. All studies except one (Leung 2009) were reported in the Chinese language. It was decided to use only the results from Leung 2009 because we were unable to verify details from the Chinese studies. The full meta-analyses are reported here, but the evidence in the GRADE table and the NMA is based only on Leung 2009.

Figure 154: % of people with undetectable HBV DNA (end of treatment)

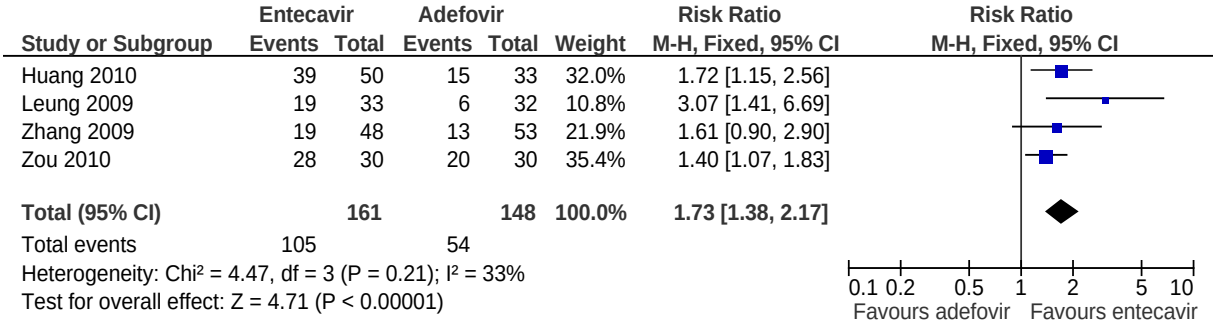


Figure 155: % of people with HBeAg seroconversion

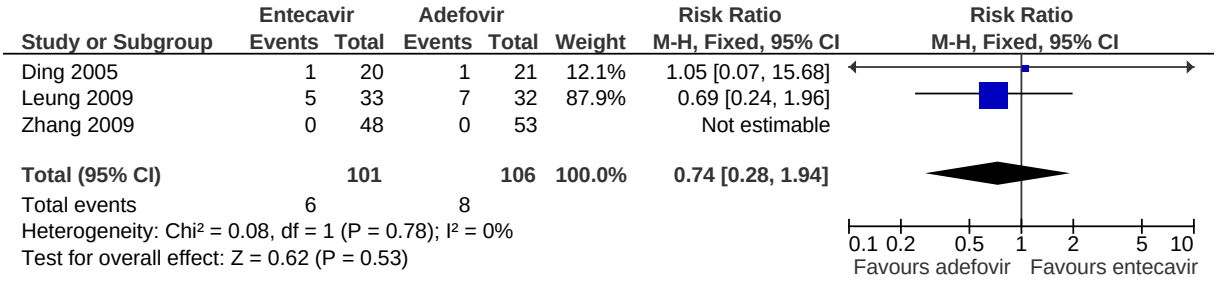


Figure 156: % of people with HBeAg loss

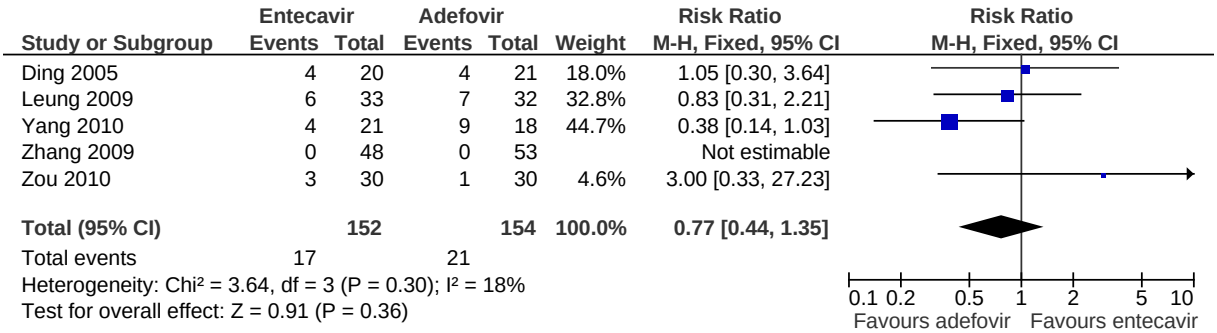
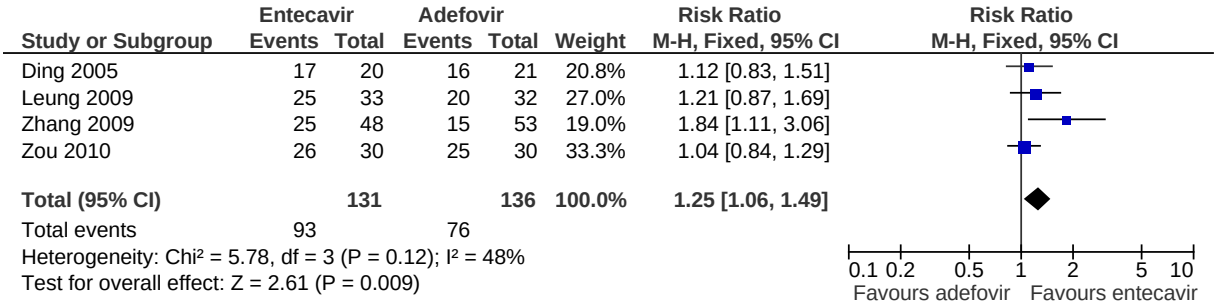


Figure 157: % of people with ALT normalisation



Comparison of telbivudine versus entecavir

Figure 158: Mean log reduction of HBV DNA at week 12 and 24 (end of treatment)

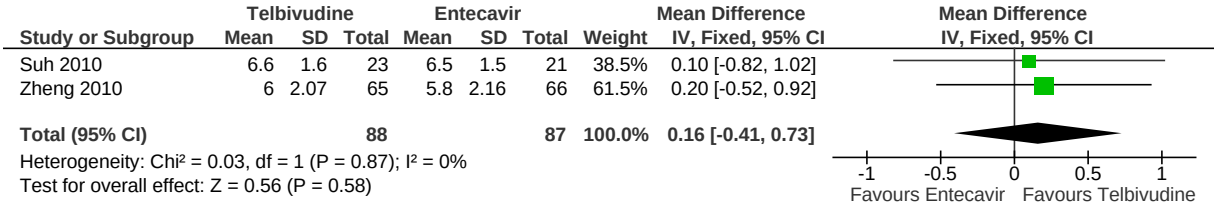


Figure 159: % with continuing detectable HBV DNA (>=500 copies/mL) at week 24 (end of treatment)

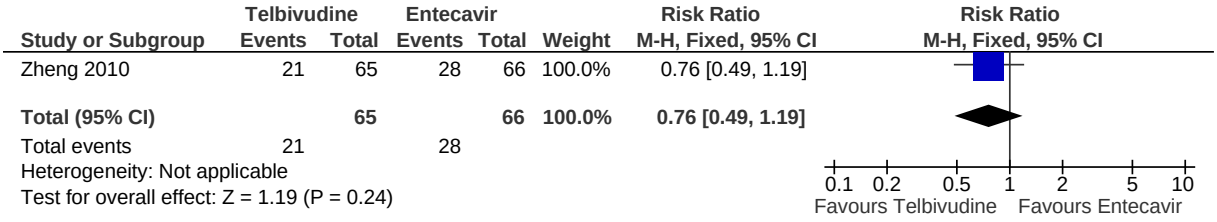


Figure 160: % with HBeAg loss at week 24 (end of treatment)

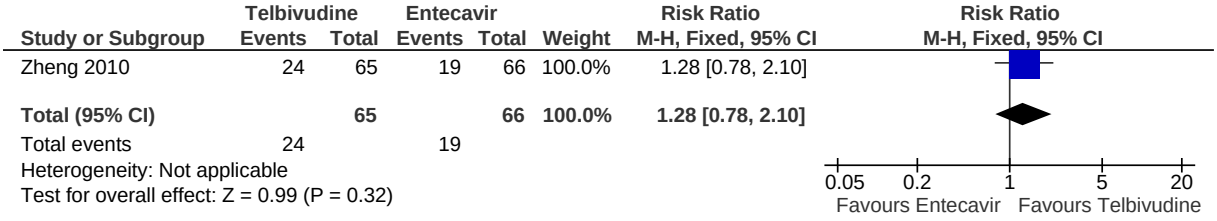


Figure 161: % with HBeAg seroconversion at week 24 (end of treatment)

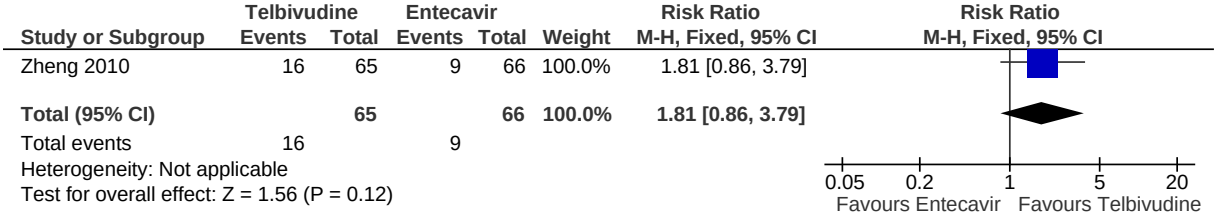
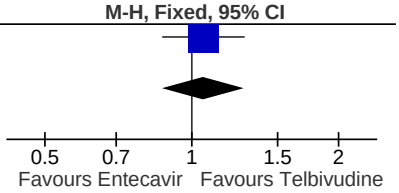


Figure 162: % with ALT normalisation at week 24 (end of treatment)

Study or Subgroup	Telbivudine Events	Total	Entecavir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zheng 2010	51	65	49	66	100.0%	1.06 [0.87, 1.28]
Total (95% CI)		**65**		**66**	**100.0%**	**1.06 [0.87, 1.28]**
Total events	51		49			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)



Comparison of entecavir + tenofovir vs entecavir alone (HBeAg positive)

Figure 163: HBV DNA <50 IU/mL at 48 weeks.

Study or Subgroup	Entecavir + tenofovir Events	Total	Entecavir alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lok 2012	158	197	128	182	100.0%	1.14 [1.01, 1.28]
Total (95% CI)		**197**		**182**	**100.0%**	**1.14 [1.01, 1.28]**
Total events	158		128			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.20 (P = 0.03)

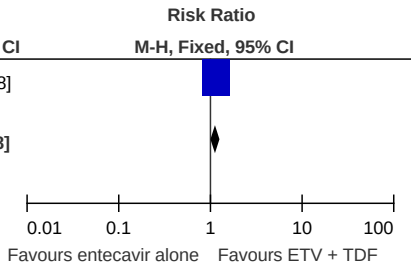


Figure 164: ALT normalisation at 48 weeks.

Study or Subgroup	Entecavir + tenofovir Events	Total	Entecavir alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lok 2012	143	197	151	182	100.0%	0.87 [0.79, 0.97]
Total (95% CI)		**197**		**182**	**100.0%**	**0.87 [0.79, 0.97]**
Total events	143		151			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.42 (P = 0.02)

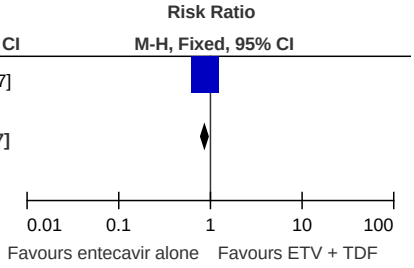


Figure 165: HBeAg loss at 48 weeks.

Study or Subgroup	Entecavir + tenofovir Events	Total	Entecavir alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lok 2012	27	138	32	126	100.0%	0.77 [0.49, 1.21]
Total (95% CI)		**138**		**126**	**100.0%**	**0.77 [0.49, 1.21]**
Total events	27		32			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)

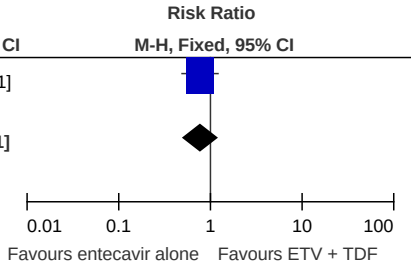


Figure 166: HBeAg seroconversion at 48 weeks.

Study or Subgroup	Entecavir + tenofovir Events	Total	Entecavir alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lok 2012	25	138	28	126	100.0%	0.82 [0.50, 1.32]
Total (95% CI)		**138**		**126**	**100.0%**	**0.82 [0.50, 1.32]**
Total events	25		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)

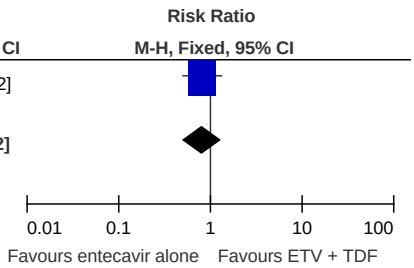


Figure 167: HBsAg loss at 48 weeks.

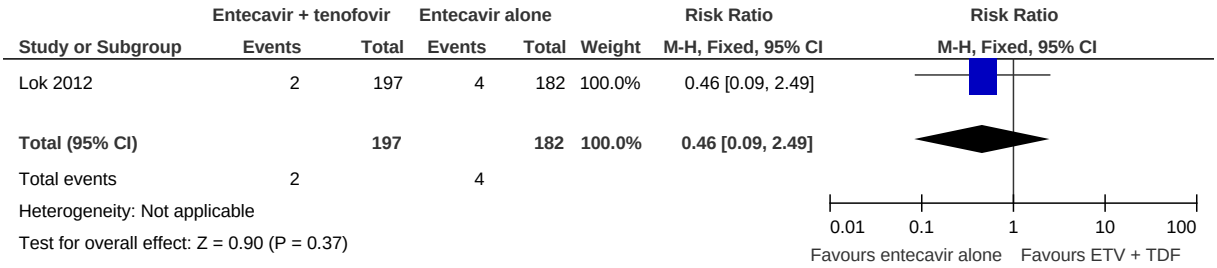


Figure 168: HBsAg seroconversion at 48 weeks.

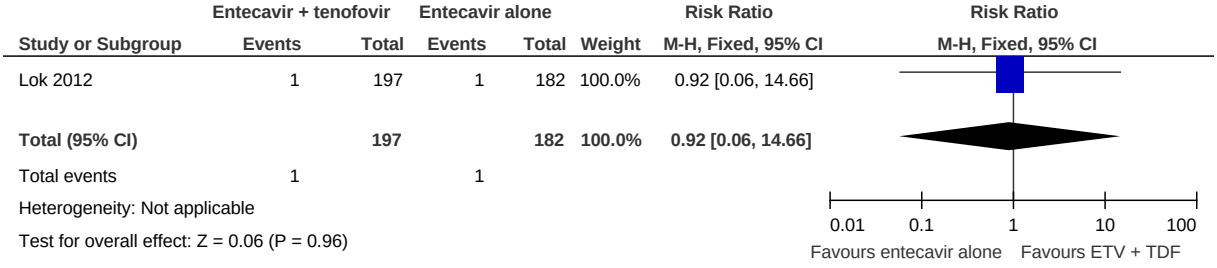


Figure 169: HBV DNA <50 IU/mL at 96 weeks.

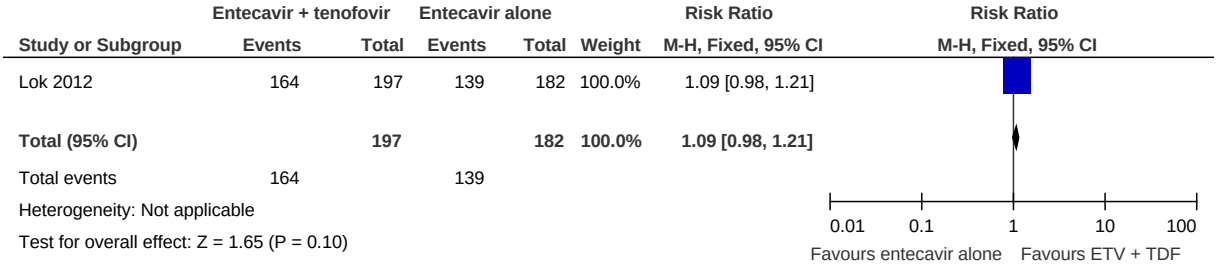


Figure 170: ALT normalisation at 96 weeks.

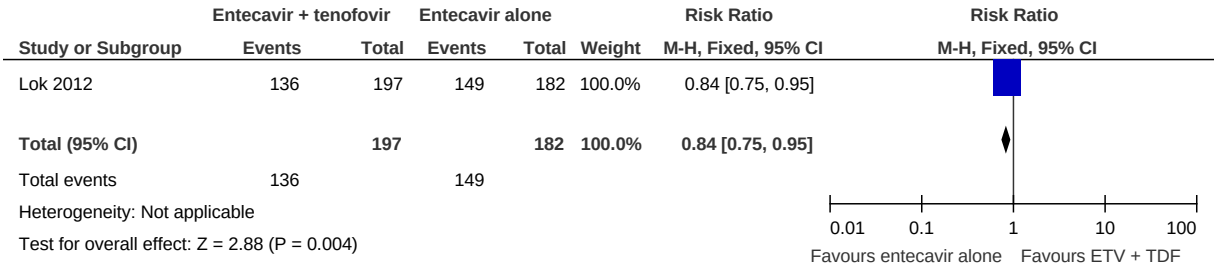


Figure 171: HBeAg loss at 96 weeks.

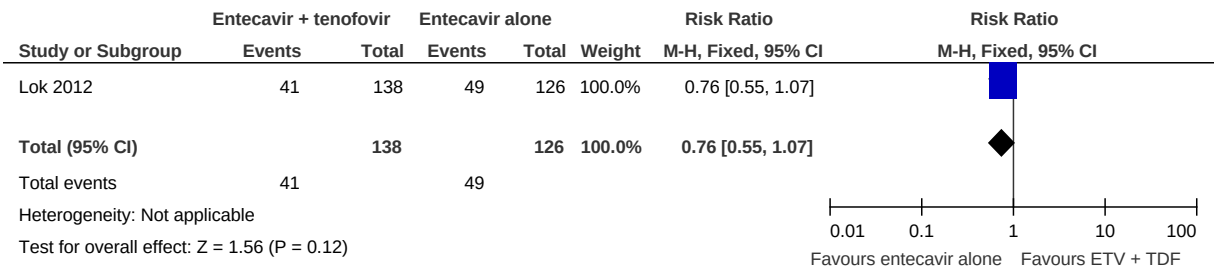


Figure 172: HBeAg seroconversion at 96 weeks.

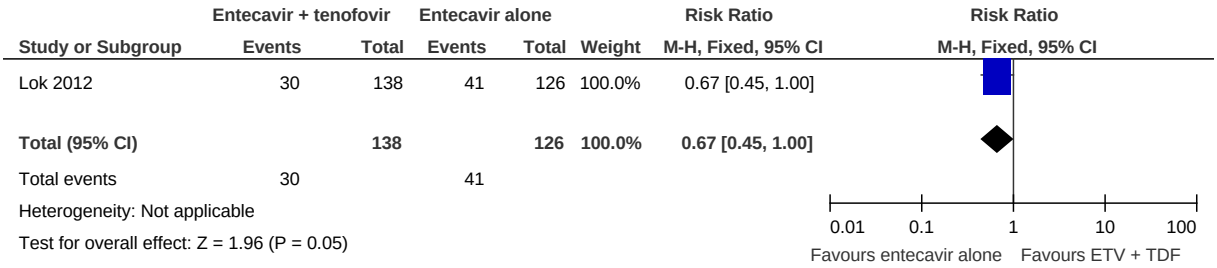


Figure 173: HBsAg loss at 96 weeks.

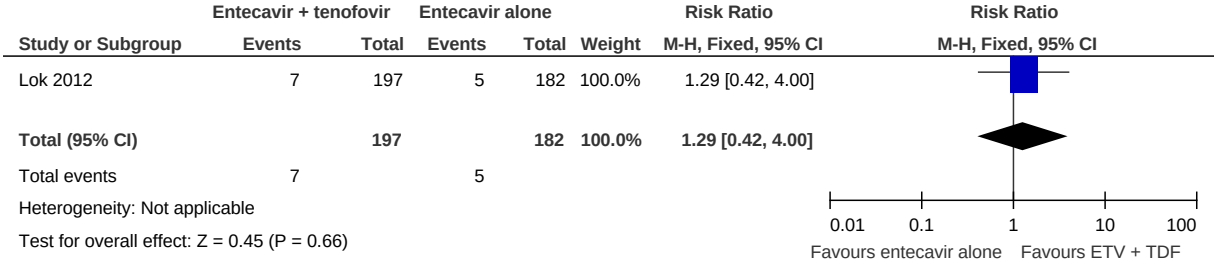


Figure 174: HBsAg seroconversion at 96 weeks

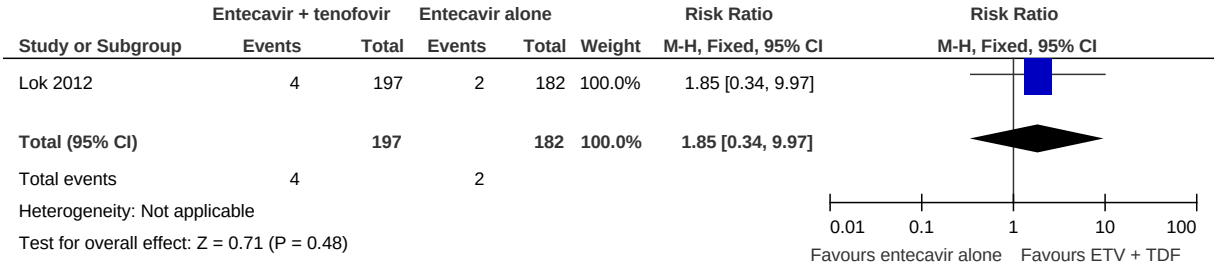


Figure 175: Virologic breakthrough at 96 weeks

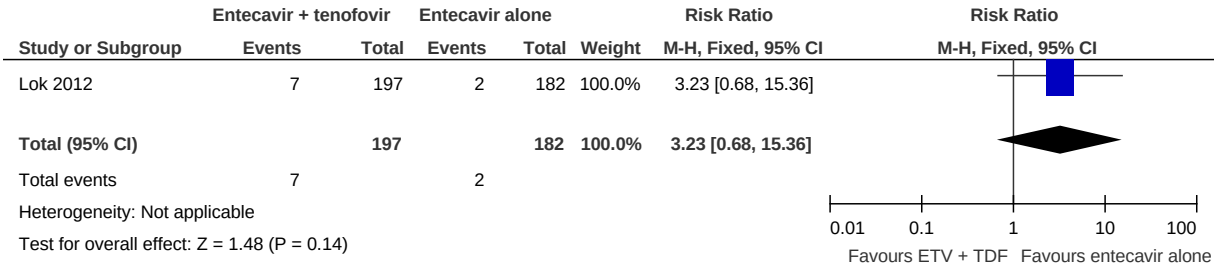
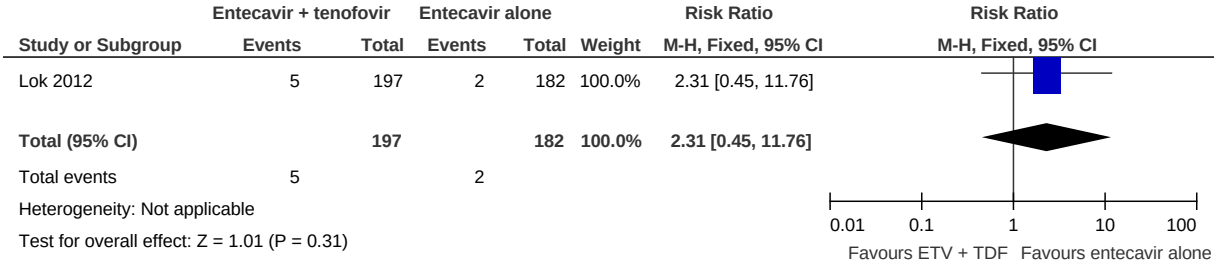


Figure 176: Discontinued due to adverse events



Comparison of Lamivudine + IFN α 2b vs placebo (HBeAg positive)

Figure 177: % of patients with undetectable HBV DNA (<1.6 pg/ml) at end of treatment.

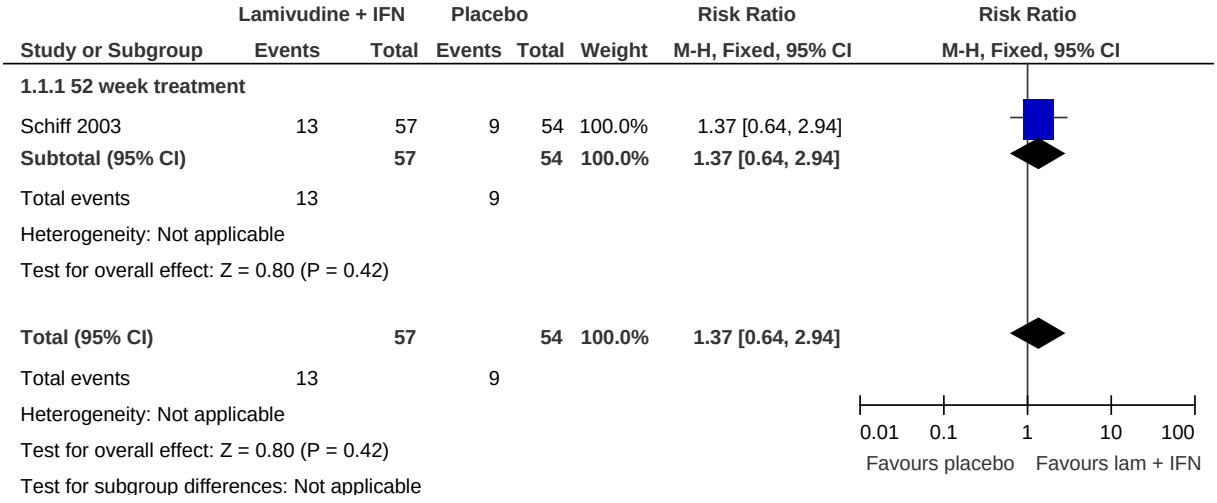


Figure 178: Loss of serum HBeAg (end of treatment).

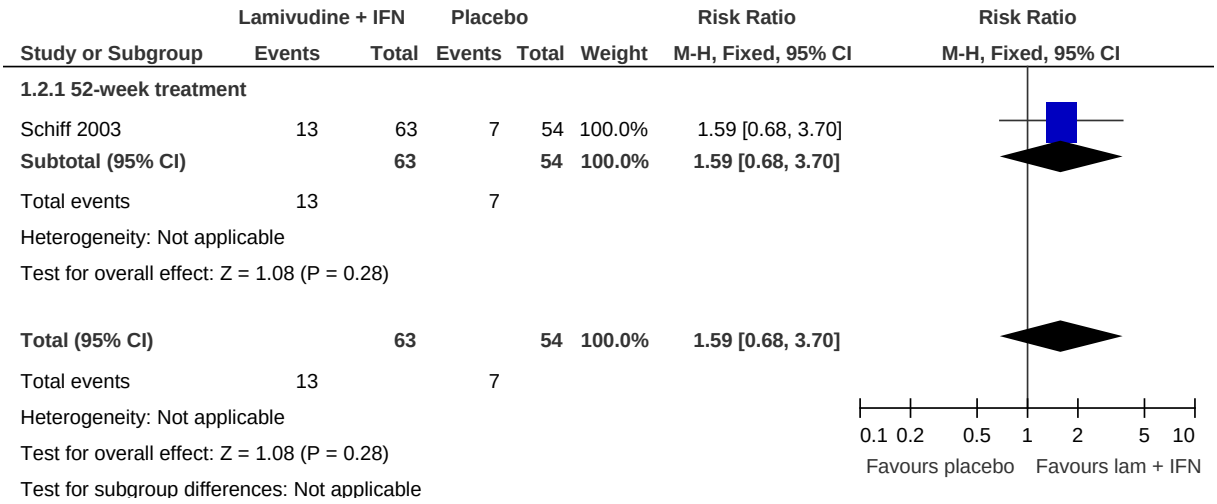


Figure 179: HBeAg seroconversion (end of treatment).

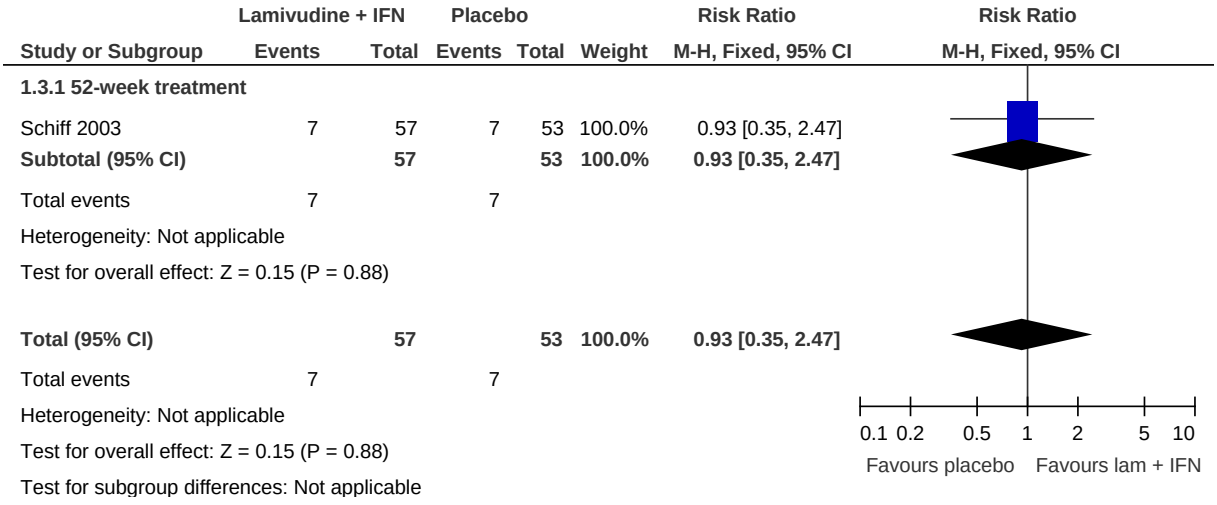


Figure 180: Histologic improvement (end of treatment).

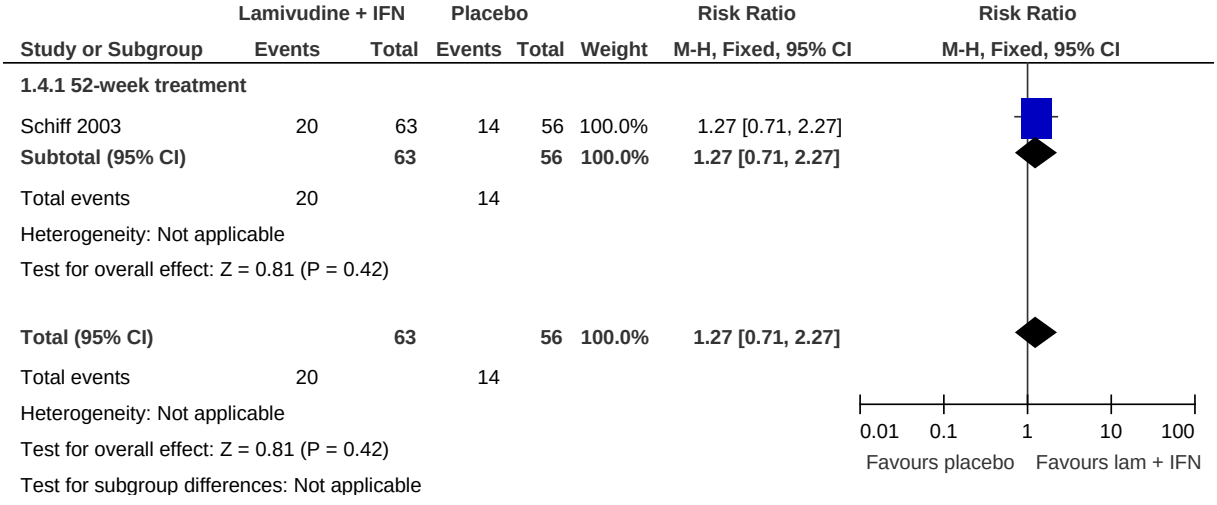
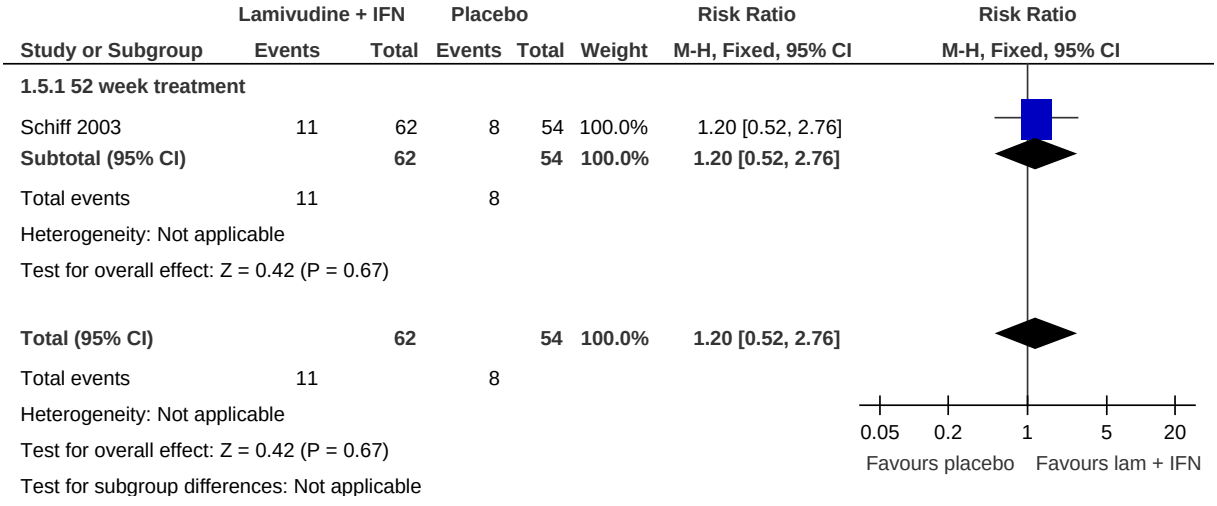


Figure 181: ALT normalization (end of treatment).



Comparison of IFNa + LAM vs IFNa (HBeAg positive)

Figure 182: Undetectable HBV DNA.

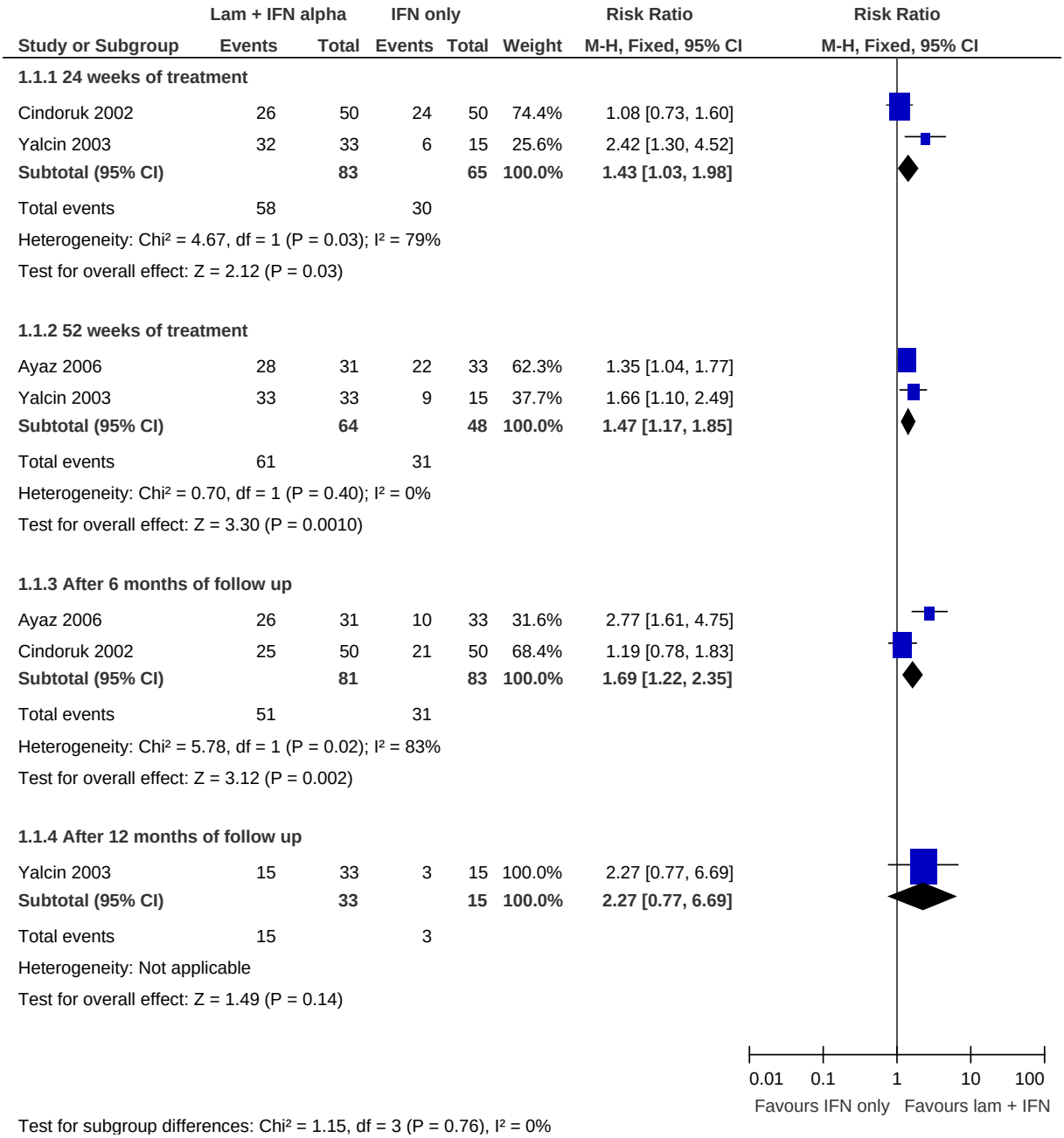


Figure 183: HBeAg seroconversion

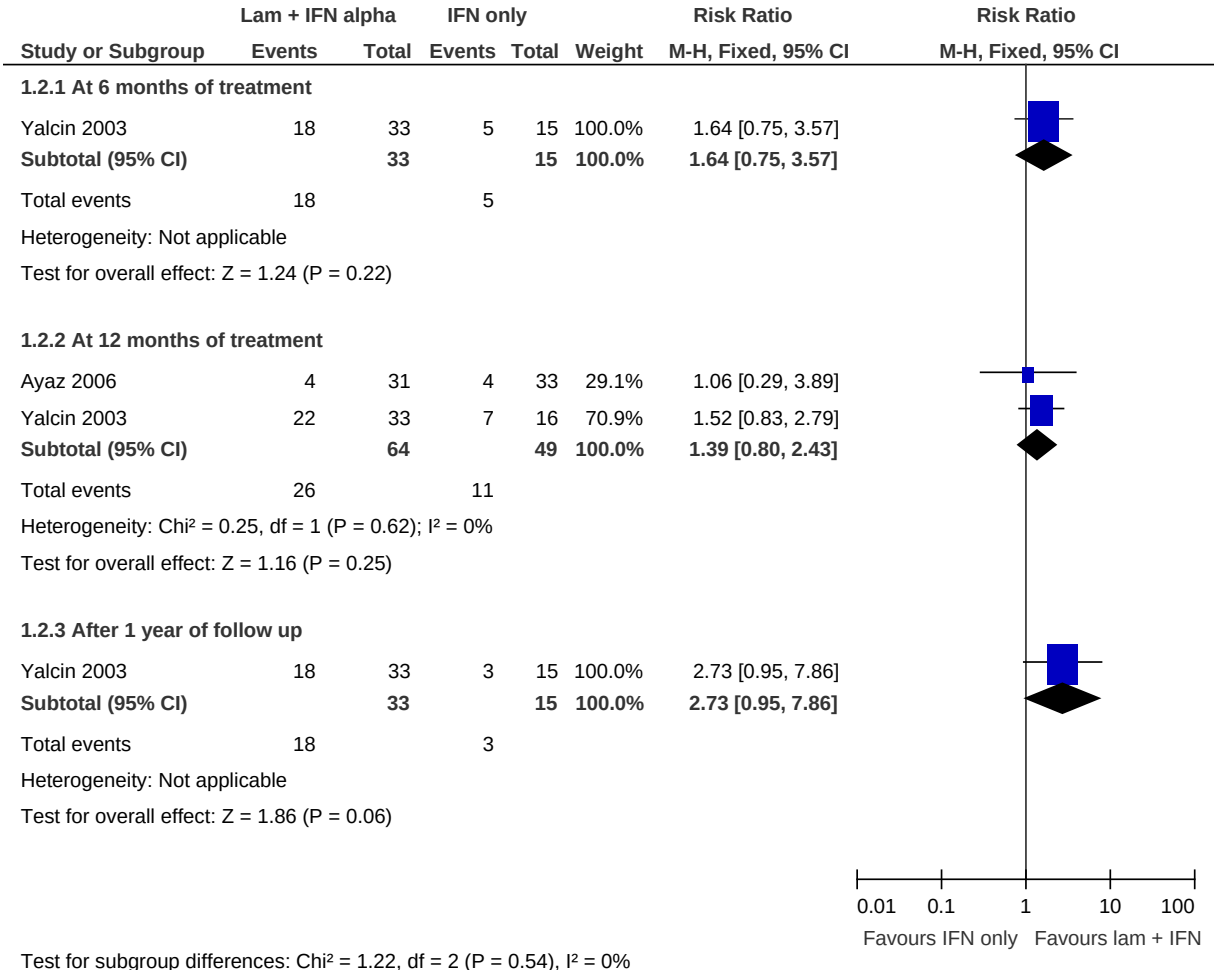


Figure 184: HBsAg loss at end of treatment.

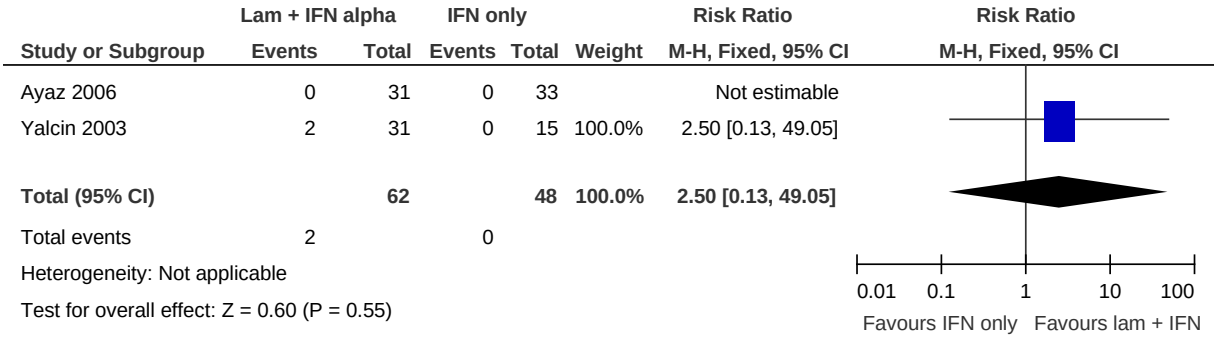


Figure 185: ALT normalisation.

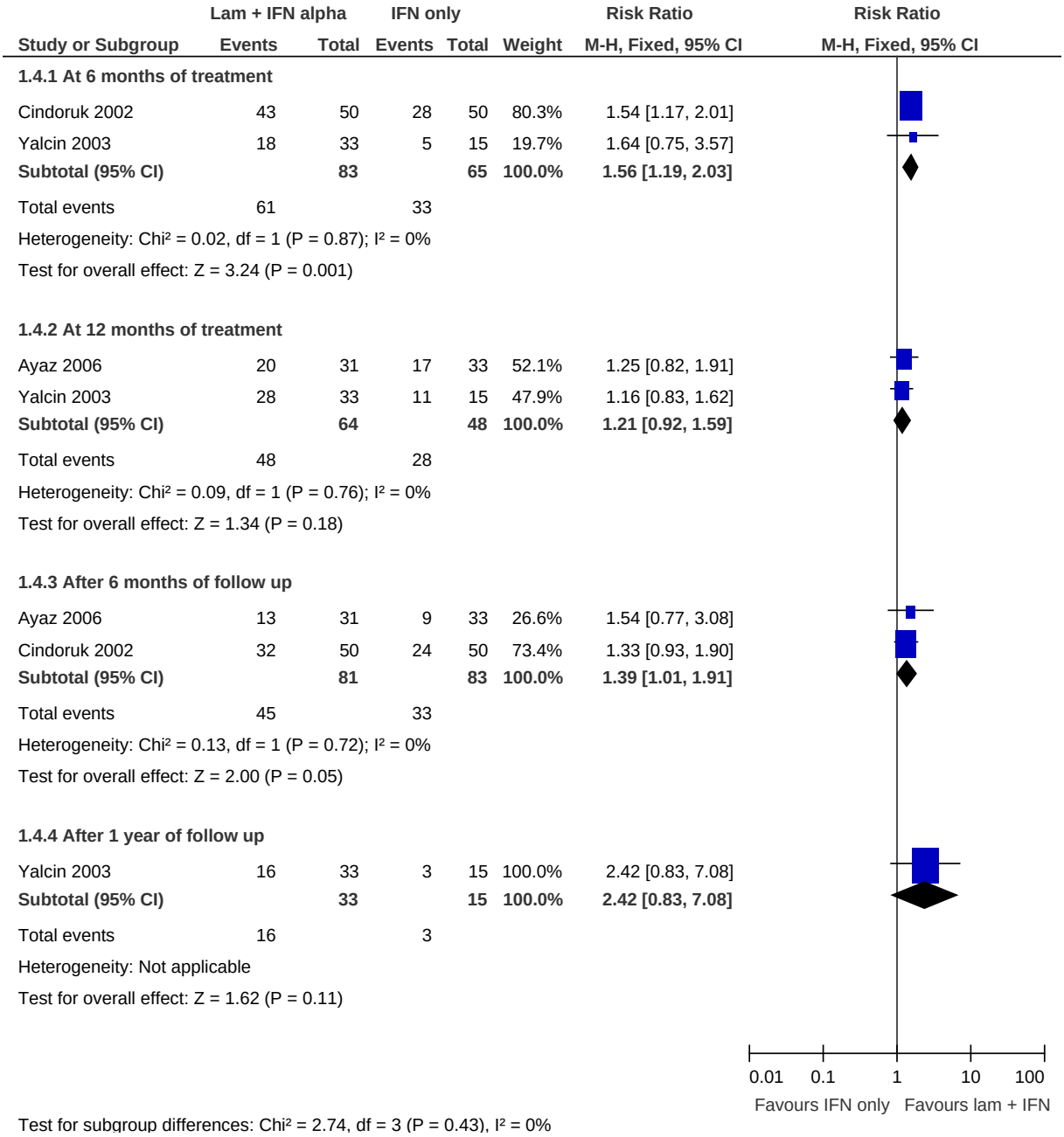
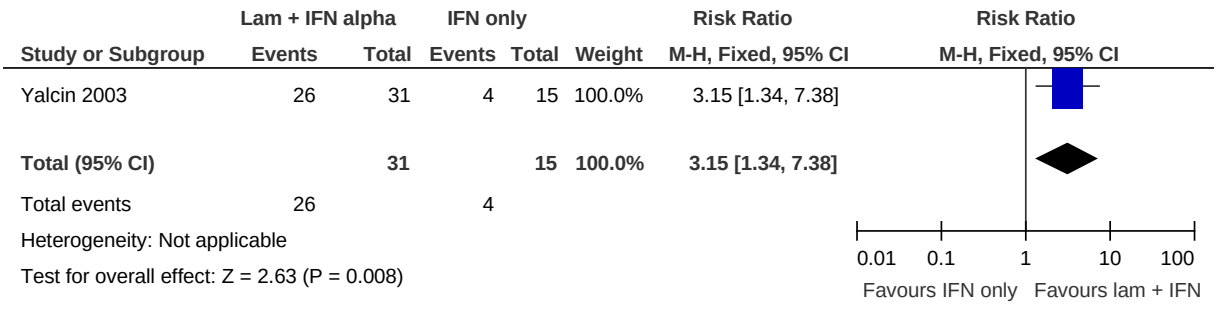


Figure 186: Histological response.



PegINF2a + LAM v PegINFa2a

Figure 187: % of people with undetectable HBV DNA (<400 copies/ml) (end of 48 weeks).

Study or Subgroup	Peg alpha-2a + Lamivudine Events	Total	Pegylated a-2a Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lau 2005	186	246	68	243	100.0%	2.70 [2.18, 3.35]
Total (95% CI)		**246**		**243**	**100.0%**	**2.70 [2.18, 3.35]**
Total events	186		68			

Heterogeneity: Not applicable
Test for overall effect: Z = 9.11 (P < 0.00001)

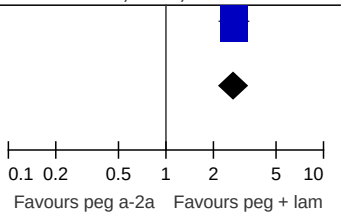


Figure 188: % of people with HBV DNA <100,000 copies/ml (end of 48 weeks).

Study or Subgroup	Peg alpha-2a + Lamivudine Events	Total	Pegylated a-2a Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lau 2005	233	246	142	243	100.0%	1.62 [1.45, 1.81]
Total (95% CI)		**246**		**243**	**100.0%**	**1.62 [1.45, 1.81]**
Total events	233		142			

Heterogeneity: Not applicable
Test for overall effect: Z = 8.60 (P < 0.00001)

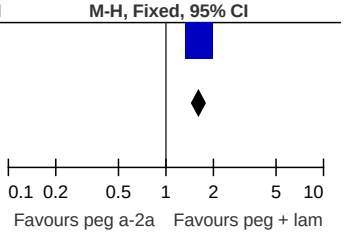


Figure 189: HBeAg seroconversion (48 weeks of treatment).

Study or Subgroup	Peg alpha-2a + Lamivudine Events	Total	Pegylated a-2a Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lau 2005	64	246	72	243	100.0%	0.88 [0.66, 1.17]
Total (95% CI)		**246**		**243**	**100.0%**	**0.88 [0.66, 1.17]**
Total events	64		72			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

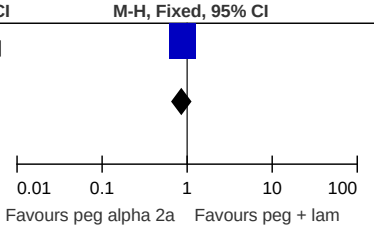


Figure 190: HBeAg loss (48 weeks of treatment).

Study or Subgroup	Peg alpha-2a + Lamivudine Events	Total	Pegylated a-2a Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lau 2005	73	246	81	243	100.0%	0.89 [0.69, 1.16]
Total (95% CI)		**246**		**243**	**100.0%**	**0.89 [0.69, 1.16]**
Total events	73		81			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)

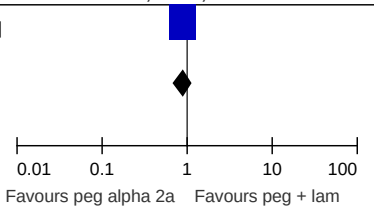


Figure 191: Normalisation of ALT (48 weeks of treatment).

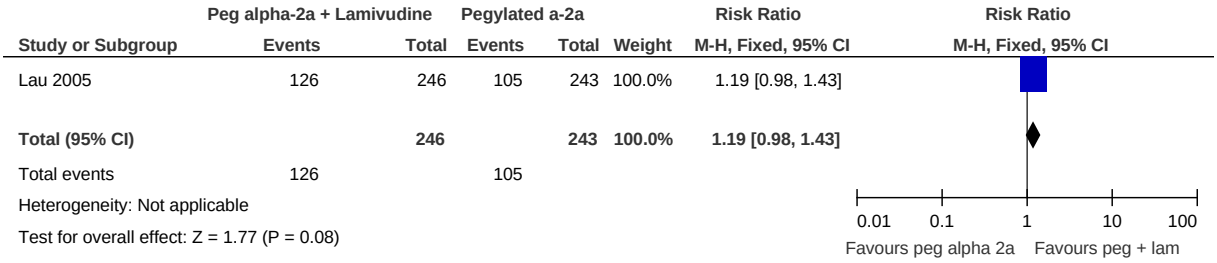


Figure 192: % of people withdrawn due to adverse events.

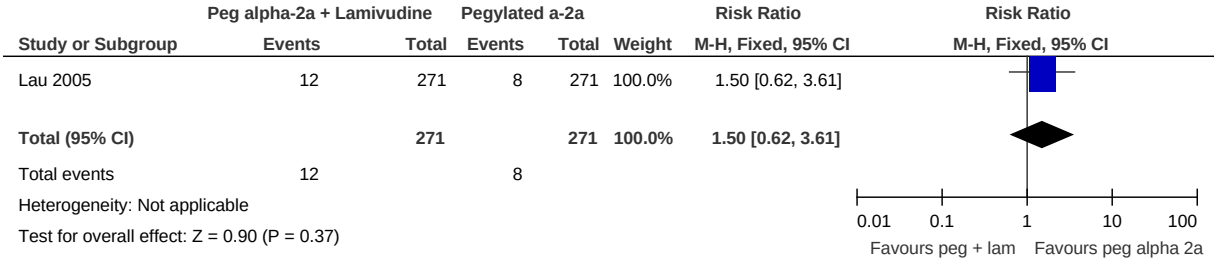


Figure 193: % of people with undetectable HBV DNA (<400 copies/ml) (24 weeks follow up)

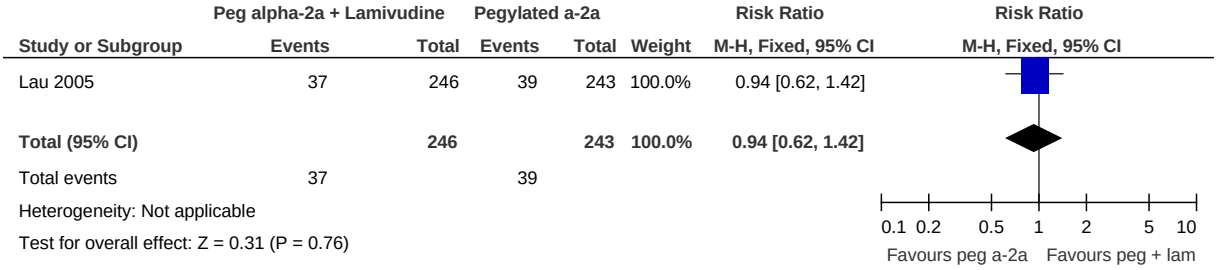


Figure 194: % of people with HBV DNA (<100,000 copies/ml) (24 weeks follow up).

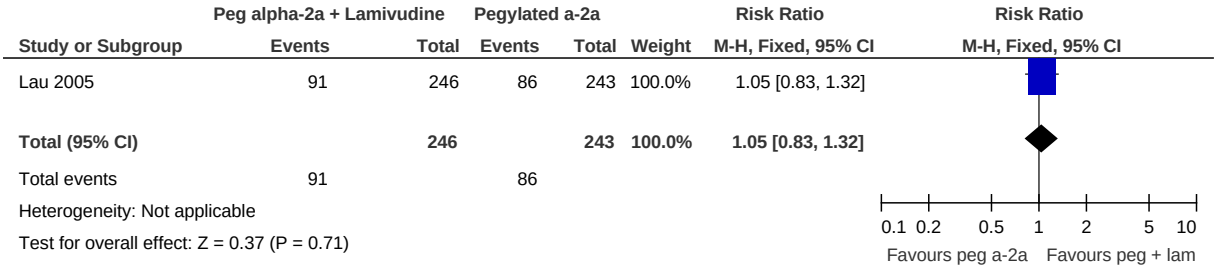


Figure 195: HBeAg seroconversion (24 weeks follow up).

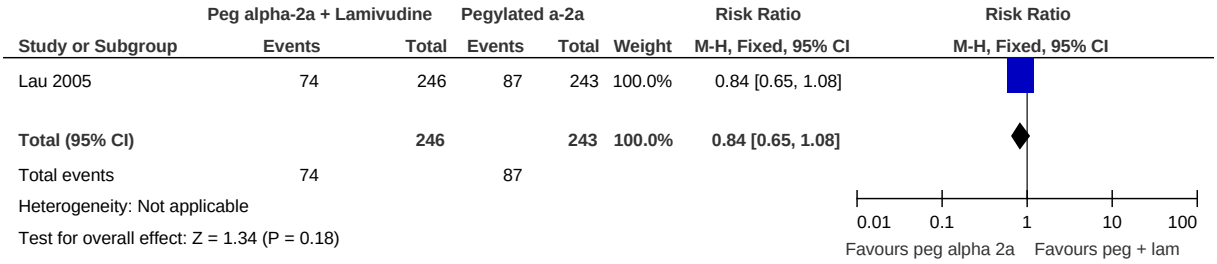


Figure 196: HBeAg loss (24 weeks follow up).

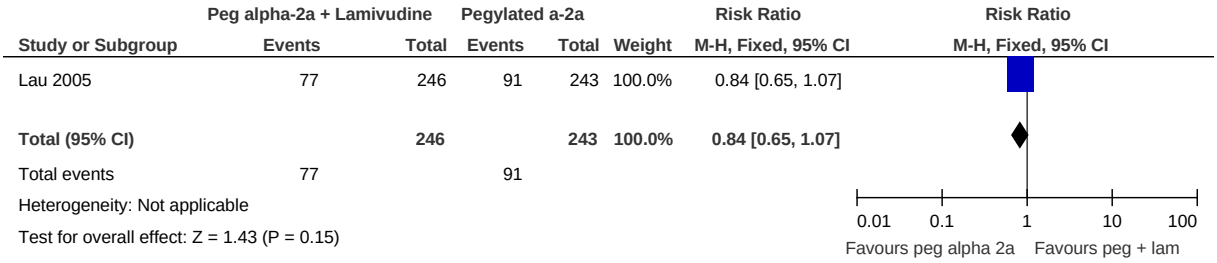
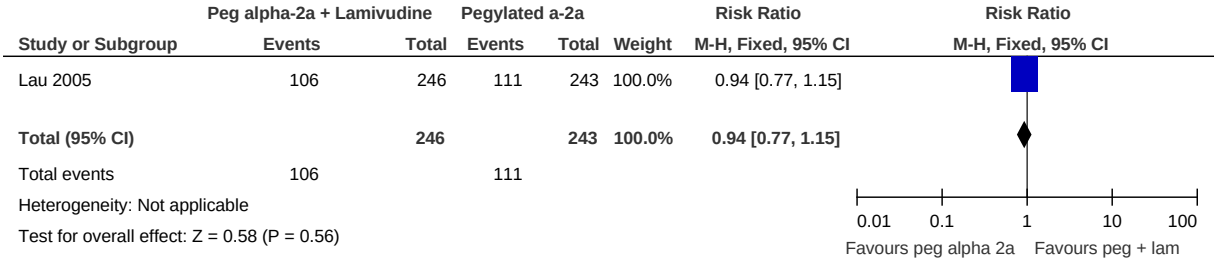


Figure 197: Normalisation of ALT (24 weeks follow up).



Pega2b + LAM v Pega2b HBeAg positive

Figure 198: HBV DNA <200,000 copies/mL at end treatment.

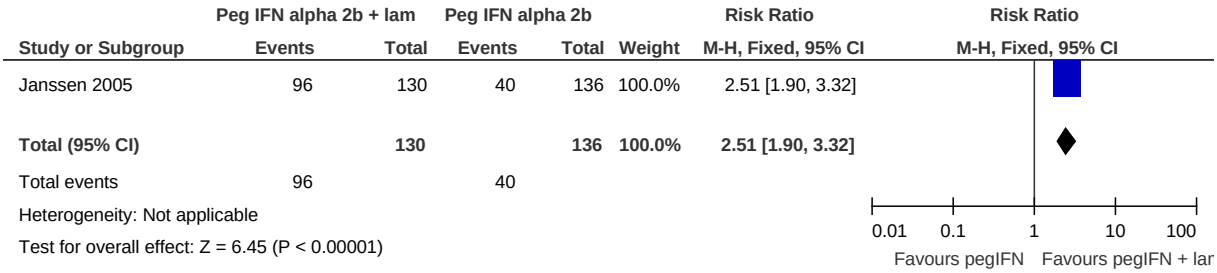


Figure 199: Undetectable HBV DNA (<400 copies/mL) at end treatment.

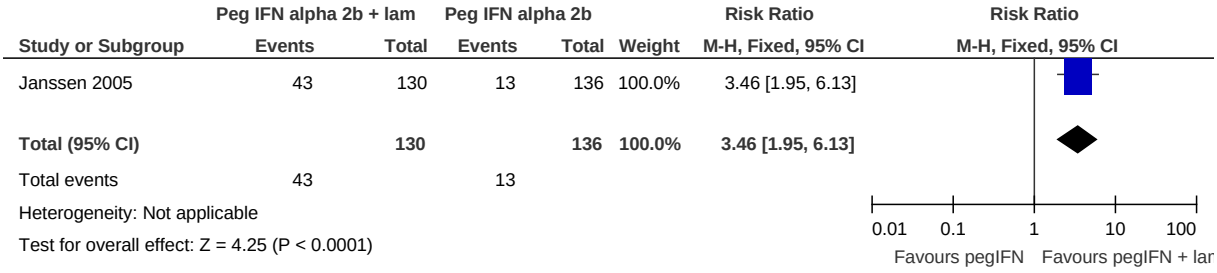


Figure 200: ALT normalisation at end treatment.

Study or Subgroup	Peg IFN alpha 2b + lam Events	Total	Peg IFN alpha 2b Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Janssen 2005	66	130	46	136	100.0%	1.50 [1.12, 2.01]
Total (95% CI)		**130**		**136**	**100.0%**	**1.50 [1.12, 2.01]**
Total events	66		46			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.75 (P = 0.006)

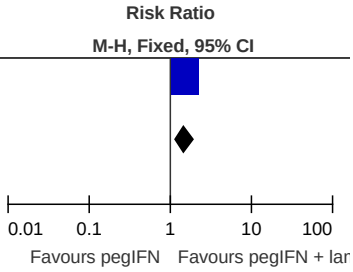


Figure 201: HBeAg loss at end treatment

Study or Subgroup	Peg IFN alpha 2b + lam Events	Total	Peg IFN alpha 2b Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Janssen 2005	57	130	40	136	100.0%	1.49 [1.08, 2.06]
Total (95% CI)		**130**		**136**	**100.0%**	**1.49 [1.08, 2.06]**
Total events	57		40			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.41 (P = 0.02)

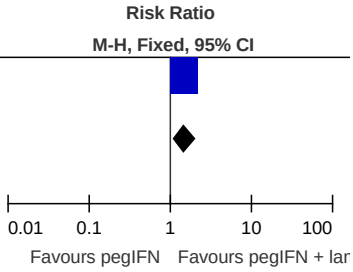


Figure 202: HBeAg seroconversion at end treatment.

Study or Subgroup	Peg IFN alpha 2b + lam Events	Total	Peg IFN alpha 2b Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Janssen 2005	33	130	30	136	100.0%	1.15 [0.75, 1.77]
Total (95% CI)		**130**		**136**	**100.0%**	**1.15 [0.75, 1.77]**
Total events	33		30			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)

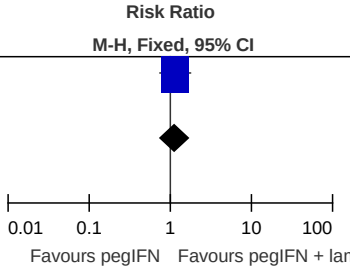


Figure 203: HBsAg loss at end treatment.

Study or Subgroup	Peg IFN alpha 2b + lam Events	Total	Peg IFN alpha 2b Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Janssen 2005	9	130	7	136	100.0%	1.35 [0.52, 3.51]
Total (95% CI)		**130**		**136**	**100.0%**	**1.35 [0.52, 3.51]**
Total events	9		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)

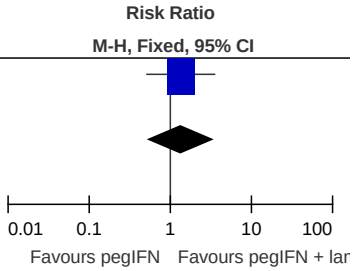


Figure 204: HBsAg seroconversion at end treatment.

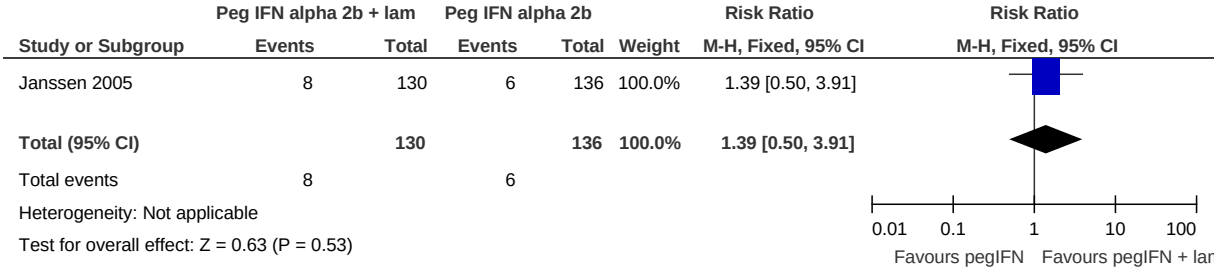


Figure 205: HBV DNA <200,000 copies/mL after 6 months follow up.

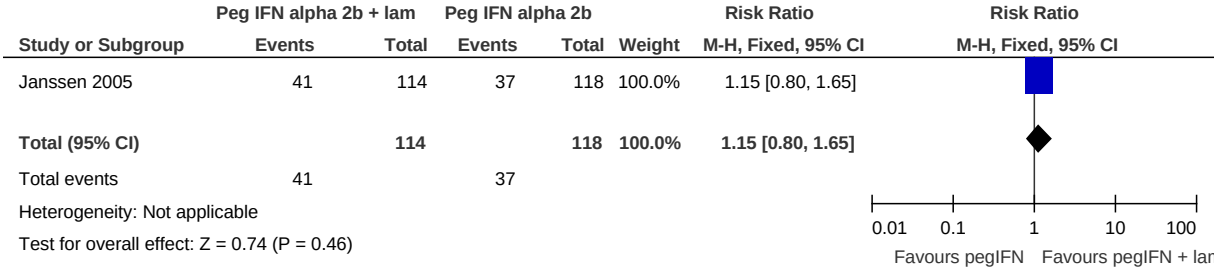


Figure 206: Undetectable HBV DNA (<400 copies/mL) after 6 months follow up.

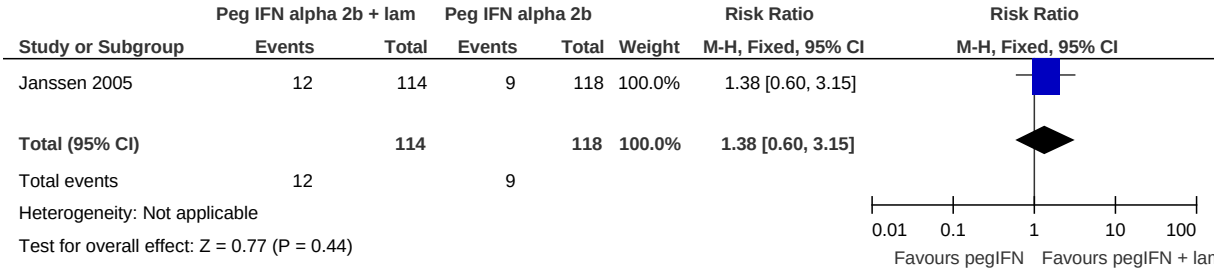


Figure 207: ALT normalisation after 6 months follow up.

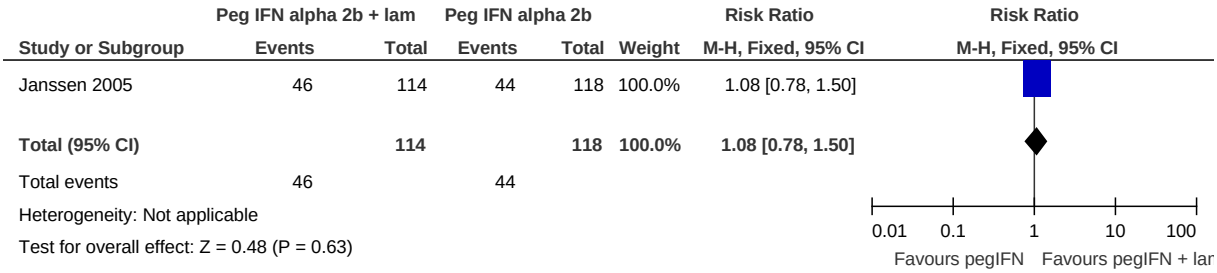


Figure 208: HBeAg loss after 6 months follow up.

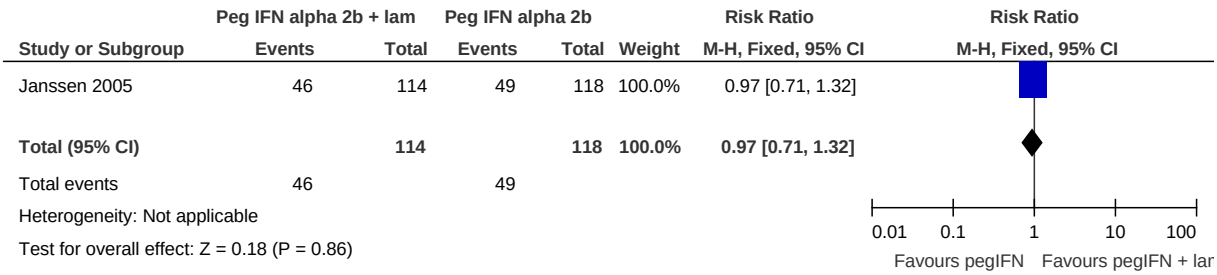


Figure 209: HBeAg seroconversion after 6 months follow up.

Study or Subgroup	Peg IFN alpha 2b + lam Events	Total	Peg IFN alpha 2b Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Janssen 2005	38	114	39	118	100.0%	1.01 [0.70, 1.45]
Total (95% CI)		**114**		**118**	**100.0%**	**1.01 [0.70, 1.45]**
Total events	38		39			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.05 (P = 0.96)

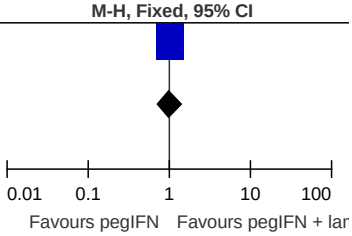


Figure 210: HBsAg loss after 6 months follow up

Study or Subgroup	Peg IFN alpha 2b + lam Events	Total	Peg IFN alpha 2b Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Janssen 2005	9	114	9	118	100.0%	1.04 [0.43, 2.51]
Total (95% CI)		**114**		**118**	**100.0%**	**1.04 [0.43, 2.51]**
Total events	9		9			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.08 (P = 0.94)

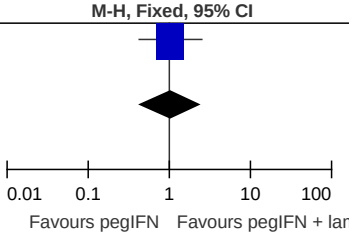
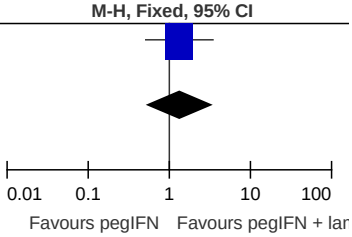


Figure 211: HBsAg seroconversion after 6 months follow up.

Study or Subgroup	Peg IFN alpha 2b + lam Events	Total	Peg IFN alpha 2b Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Janssen 2005	9	114	7	118	100.0%	1.33 [0.51, 3.45]
Total (95% CI)		**114**		**118**	**100.0%**	**1.33 [0.51, 3.45]**
Total events	9		7			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.59 (P = 0.56)



IFNalpha-2b + LAM vs LAM (HBeAg positive)

Figure 212: Undetectable HBV DNA.

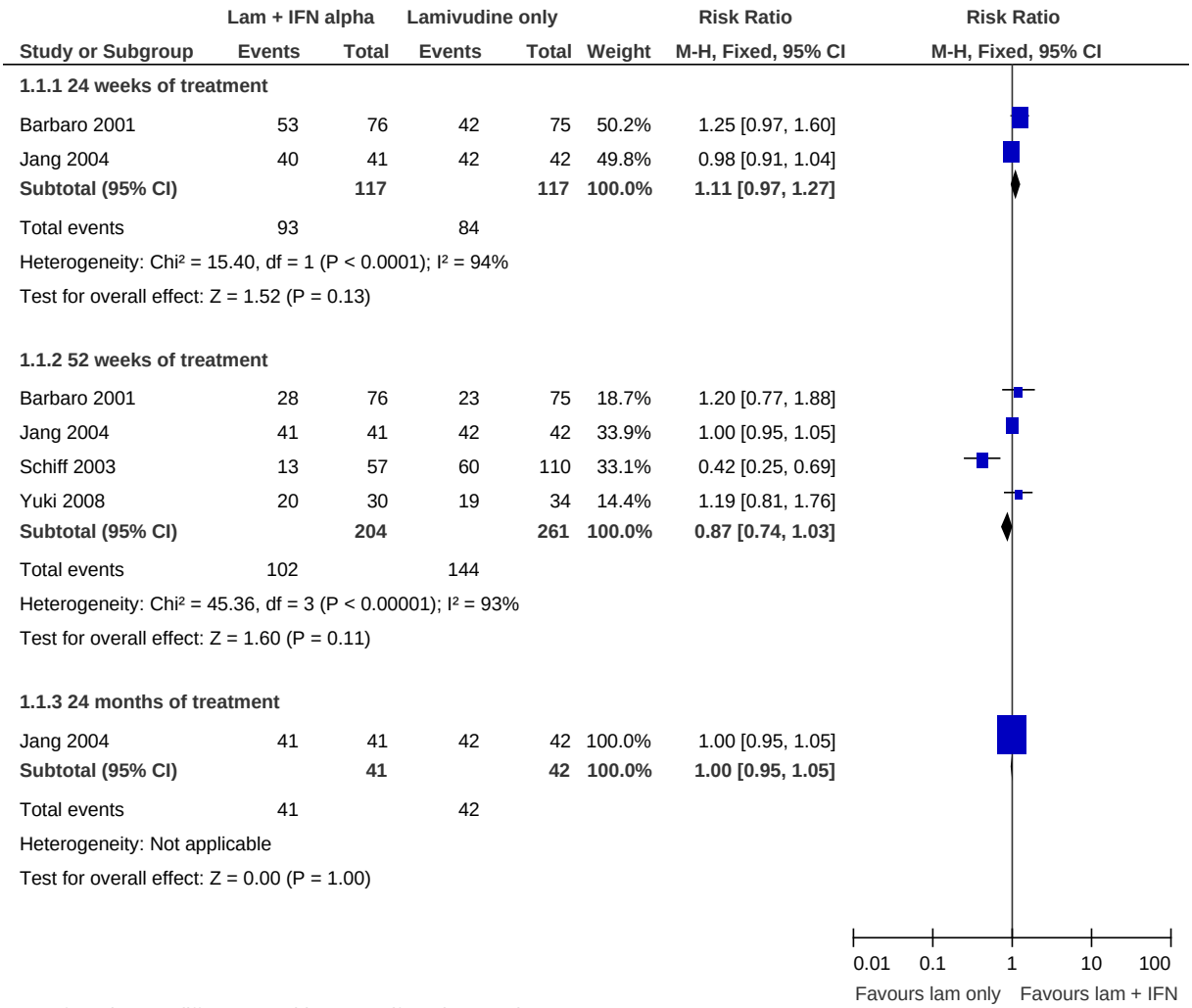


Figure 213: Viral breakthrough during treatment.

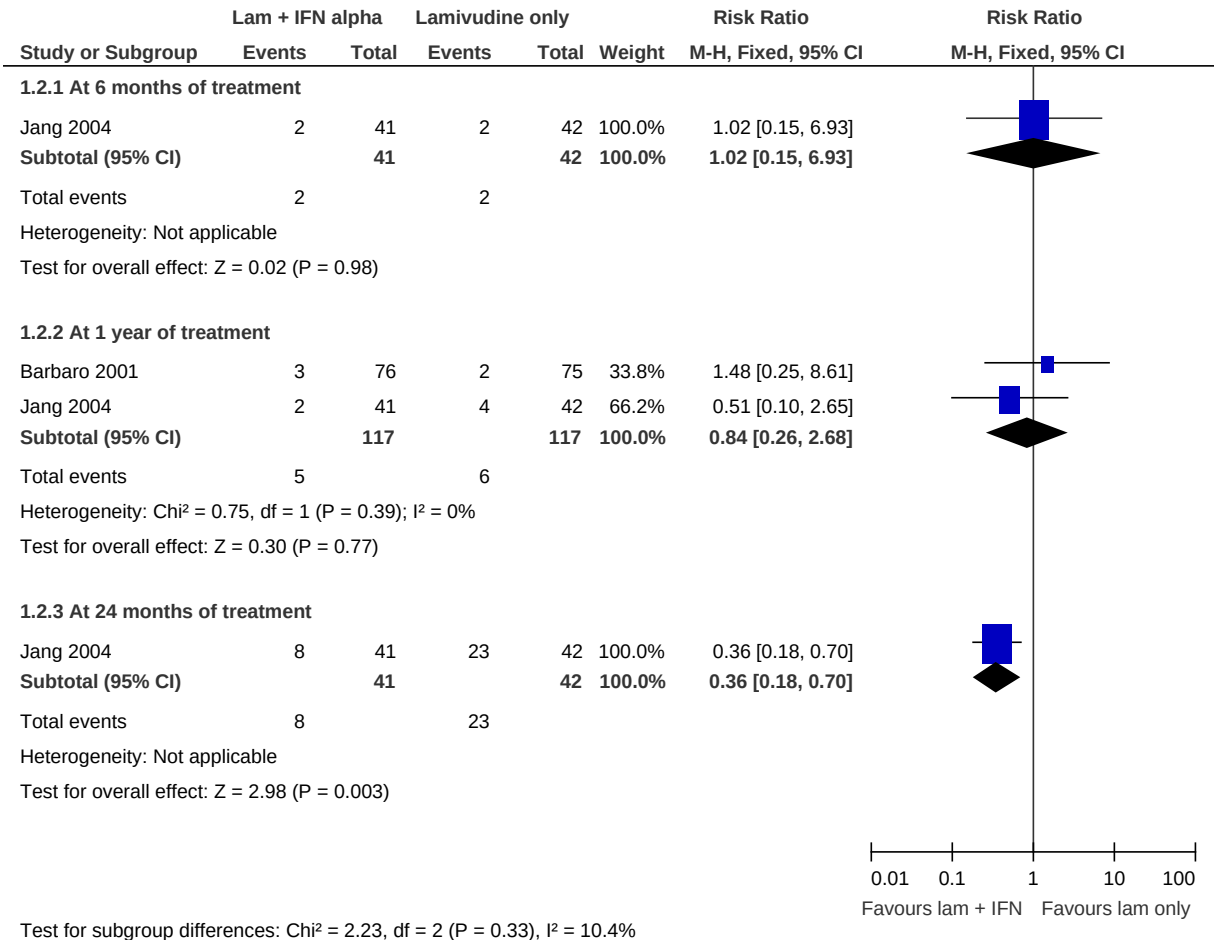


Figure 214: HBeAg loss

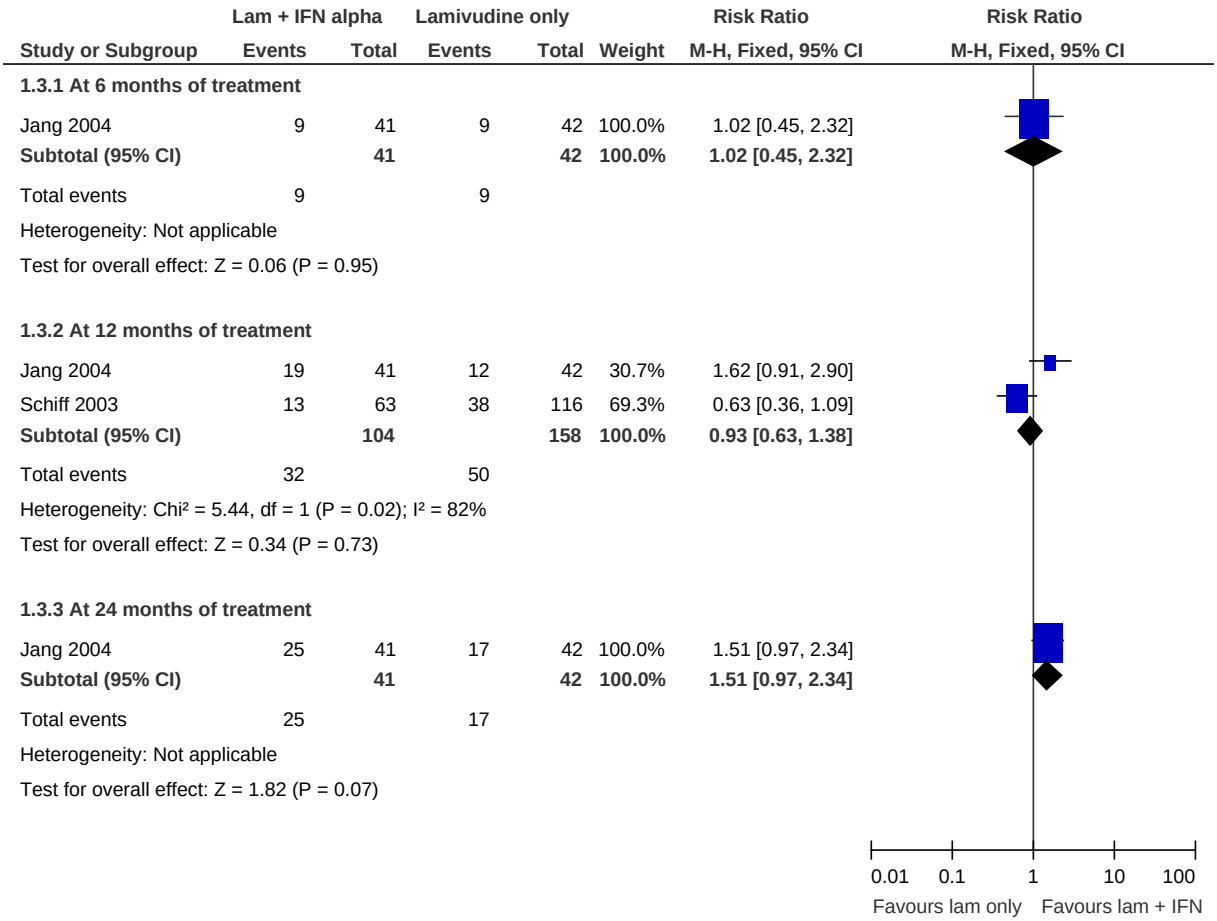


Figure 215: HBeAg seroconversion.

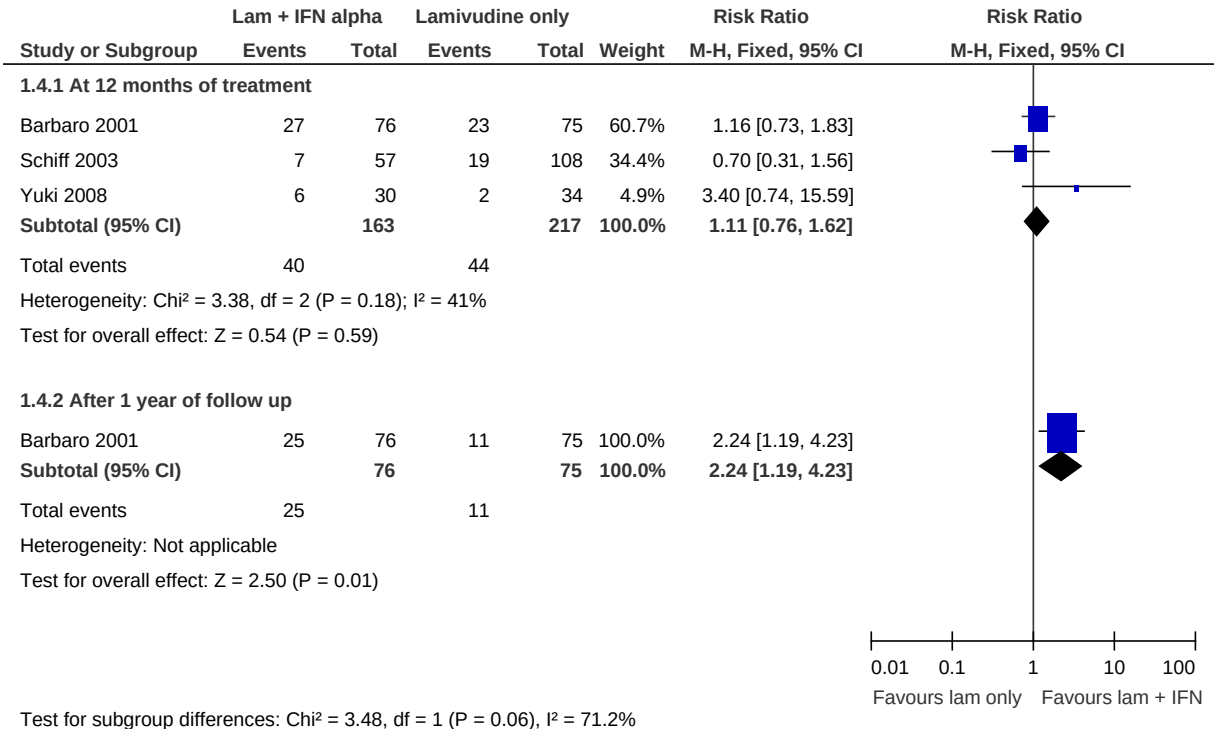


Figure 216: HBsAg loss at end of treatment.

Study or Subgroup	Lam + IFN alpha Events	Total	Lamivudine only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barbaro 2001	0	76	0	75		Not estimable
Schiff 2003	4	63	2	119	100.0%	3.78 [0.71, 20.06]
Total (95% CI)		**139**		**194**	**100.0%**	**3.78 [0.71, 20.06]**
Total events	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.56 (P = 0.12)						

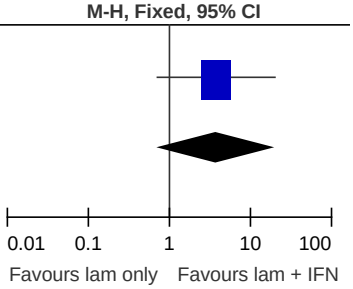


Figure 217: ALT normalisation.

Study or Subgroup	Lam + IFN alpha Events	Total	Lamivudine only Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 At 6 months of treatment						
Jang 2004	37	41	41	42	100.0%	0.92 [0.83, 1.03]
Subtotal (95% CI)		**41**		**42**	**100.0%**	**0.92 [0.83, 1.03]**
Total events	37		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						
1.6.2 At 12 months of treatment						
Jang 2004	41	41	42	42	44.4%	1.00 [0.95, 1.05]
Schiff 2003	11	62	51	115	37.8%	0.40 [0.23, 0.71]
Yuki 2008	26	30	18	34	17.8%	1.64 [1.16, 2.32]
Subtotal (95% CI)		**133**		**191**	**100.0%**	**0.89 [0.75, 1.05]**
Total events	78		111			
Heterogeneity: Chi² = 45.03, df = 2 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 1.39 (P = 0.17)						
1.6.3 At 24 months of treatment						
Jang 2004	41	41	42	42	100.0%	1.00 [0.95, 1.05]
Subtotal (95% CI)		**41**		**42**	**100.0%**	**1.00 [0.95, 1.05]**
Total events	41		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.6.4 1 year follow up						
Barbaro 2001	28	76	17	75	100.0%	1.63 [0.97, 2.71]
Subtotal (95% CI)		**76**		**75**	**100.0%**	**1.63 [0.97, 2.71]**
Total events	28		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
Test for subgroup differences: Chi² = 6.81, df = 3 (P = 0.08), I² = 56.0%						

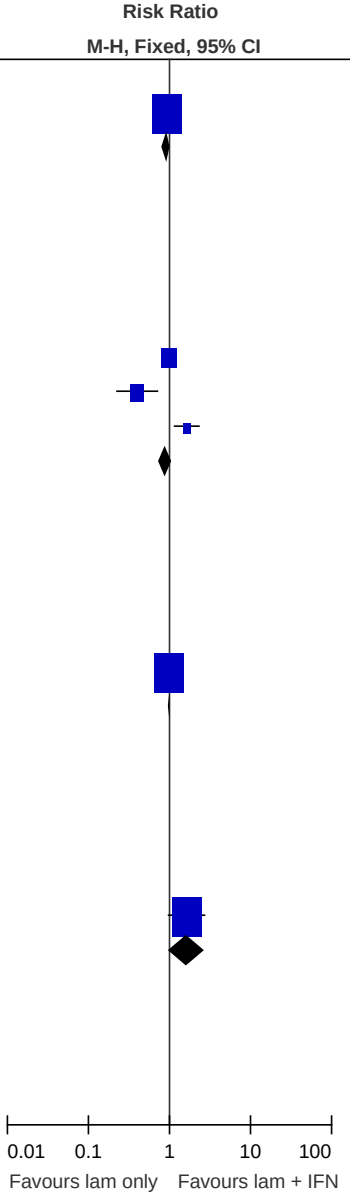


Figure 218: Genotypic resistance during treatment.

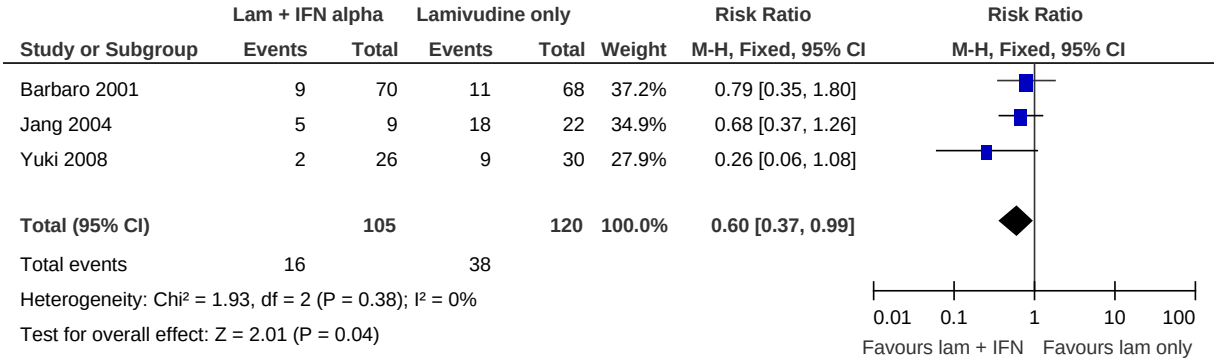
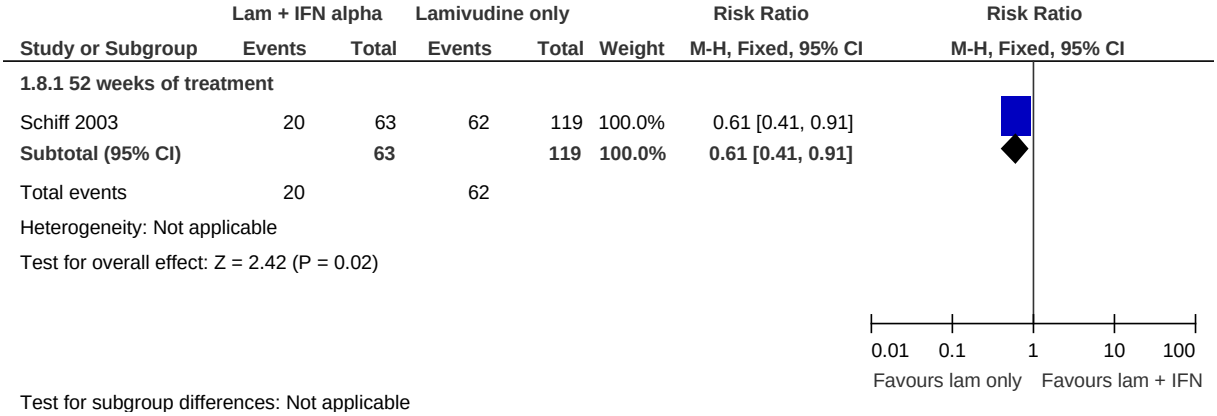


Figure 219: Histological response.



PegINFalpha 2a + LAM v LAM

Figure 220: % of people with undetectable HBV DNA (<400 copies/ml) (end of 48 weeks).

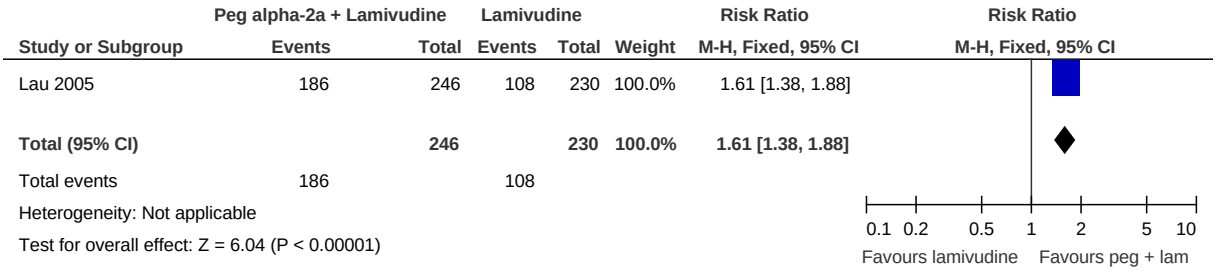


Figure 221: % of people with HBV DNA (<100,000 copies/ml) (end of 48 weeks).

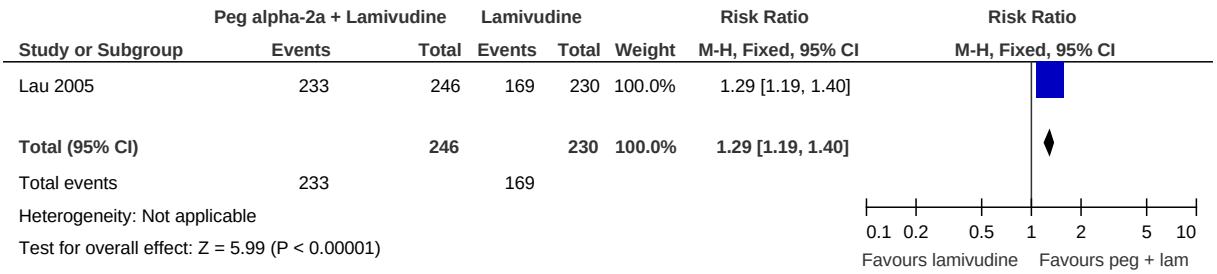


Figure 222: HBeAg seroconversion (48 weeks of treatment).

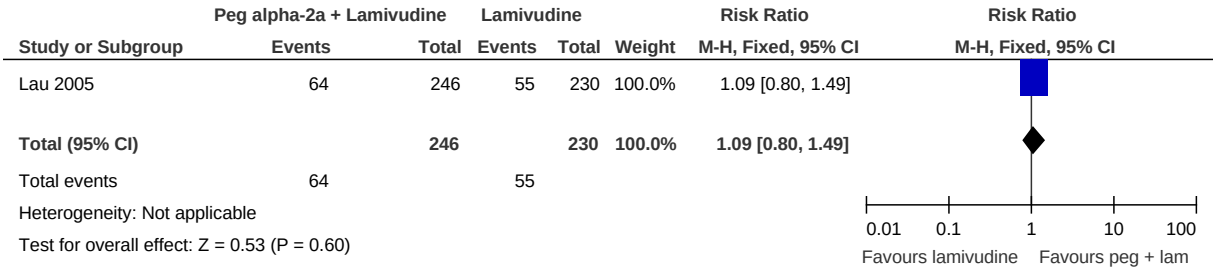


Figure 223: HBeAg loss (48 weeks of treatment).

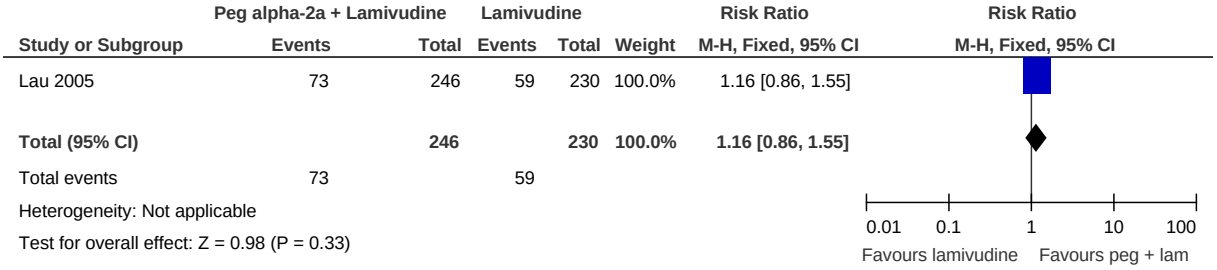


Figure 224: Normalisation of ALT (48 weeks of treatment).

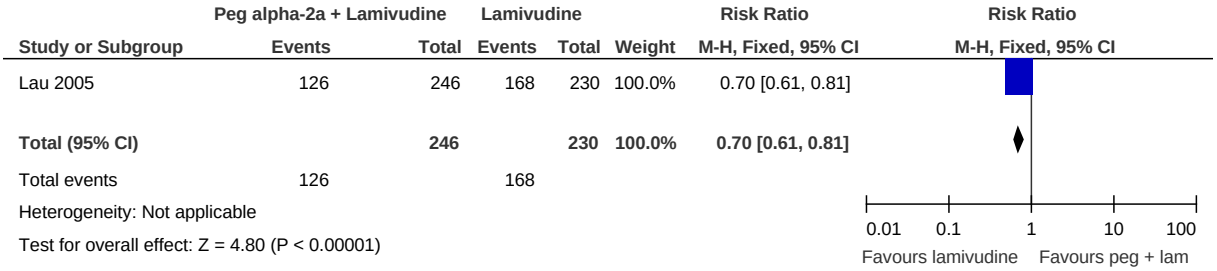


Figure 225: % of people withdrawn due to adverse events

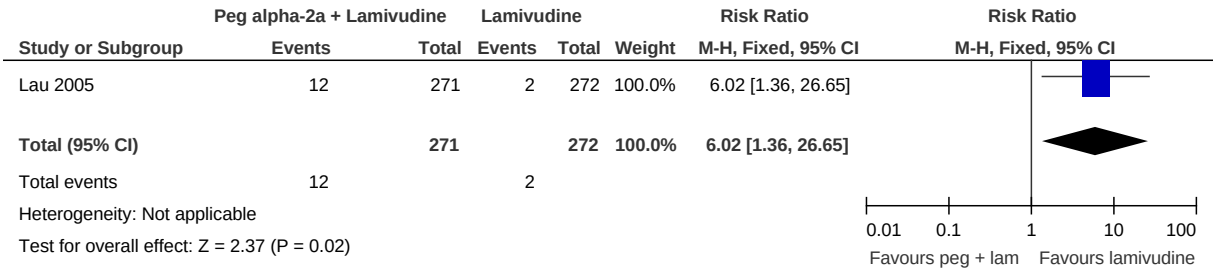


Figure 226: % of people with undetectable HBV DNA (<400 copies/ml) (24 weeks follow up

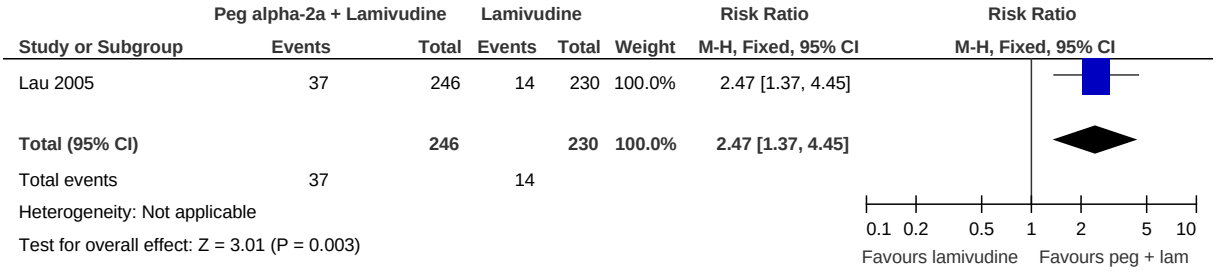


Figure 227: % of people with HBV DNA (<100,000 copies/ml) (24 weeks follow up).

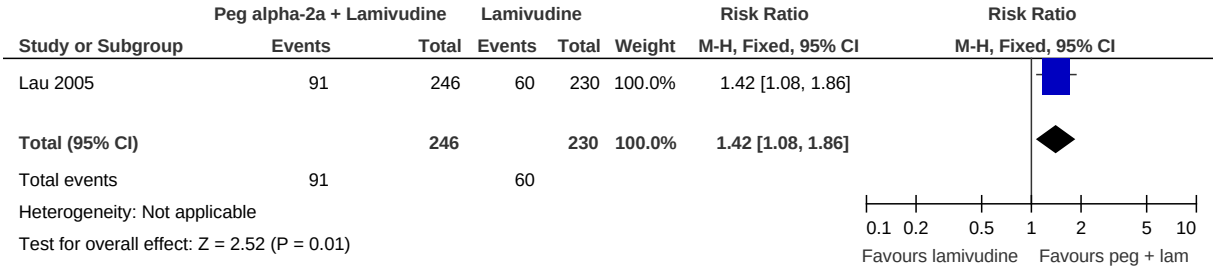


Figure 228: HBeAg seroconversion (24 weeks follow up).

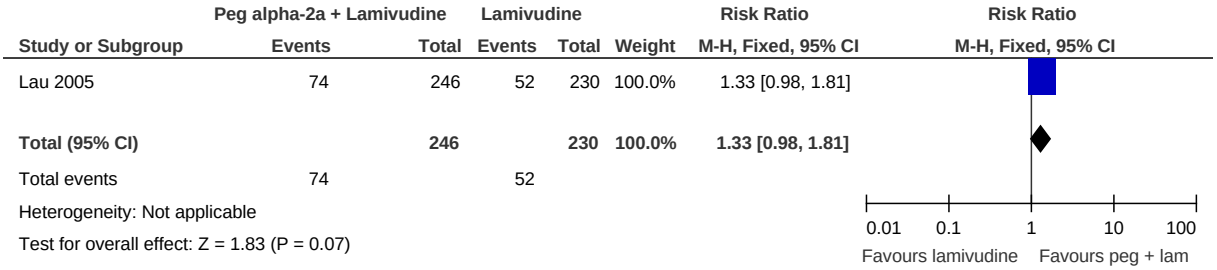


Figure 229: HBeAg loss (24 weeks follow up).

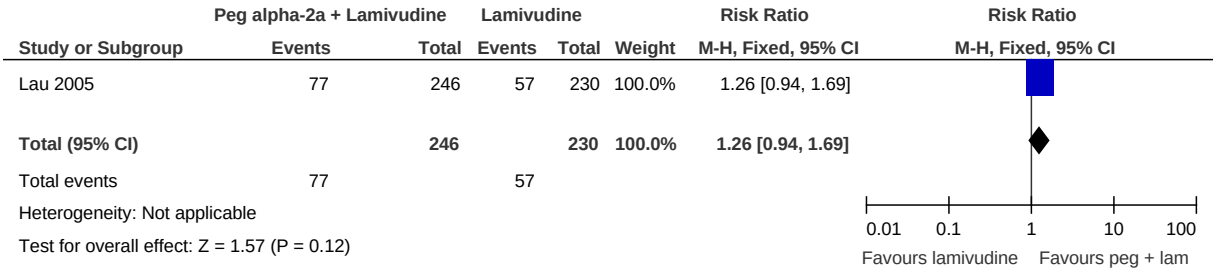
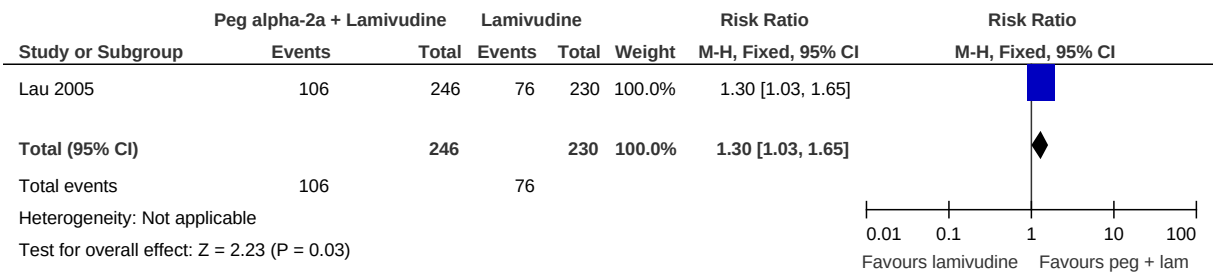


Figure 230: Normalisation of ALT (24 weeks follow up



PegINFalpha2b + LAM v LAM

Figure 231: HBV DNA <100 copies/mL at end treatment.

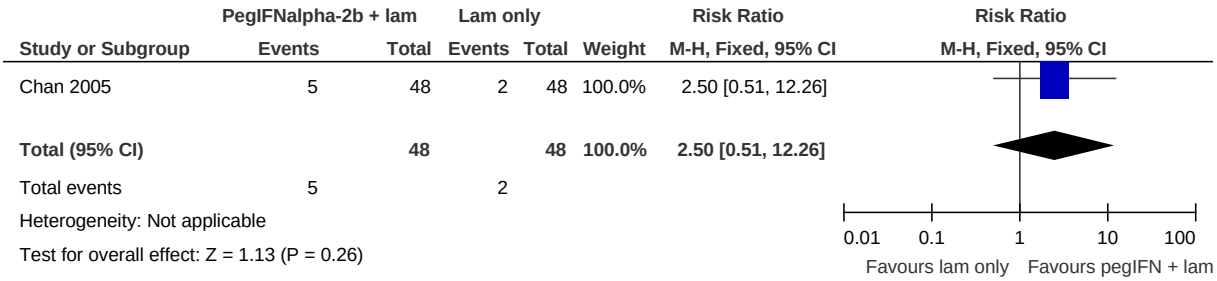


Figure 232: Resistance at end treatment.

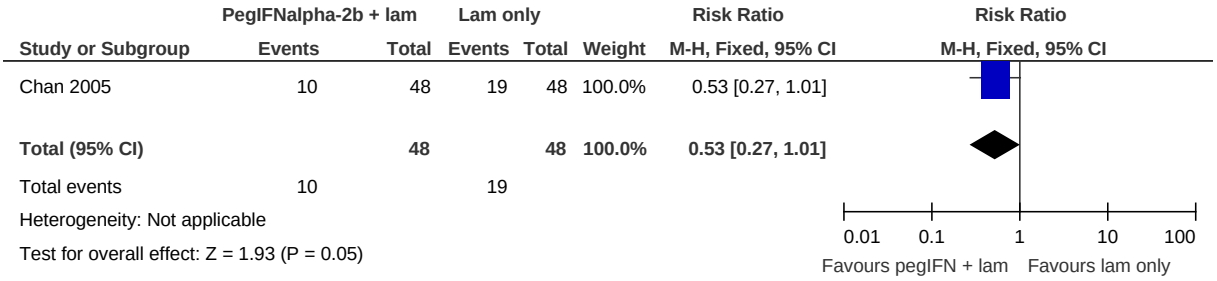


Figure 233: ALT normalisation at end treatment.

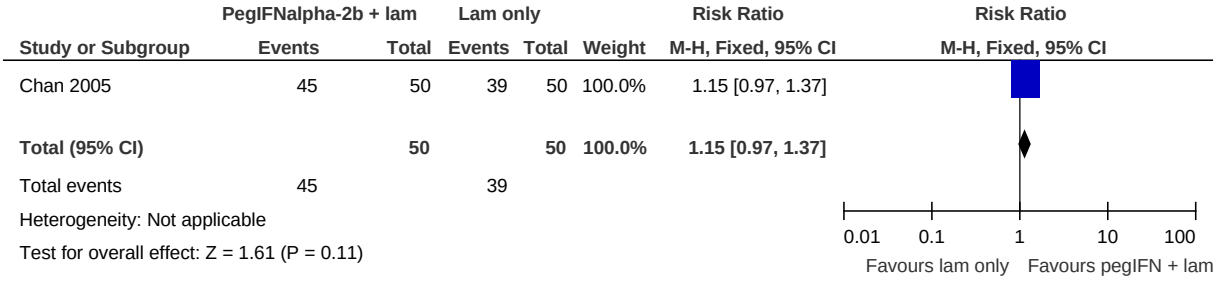


Figure 234: Histological improvement at end treatment.

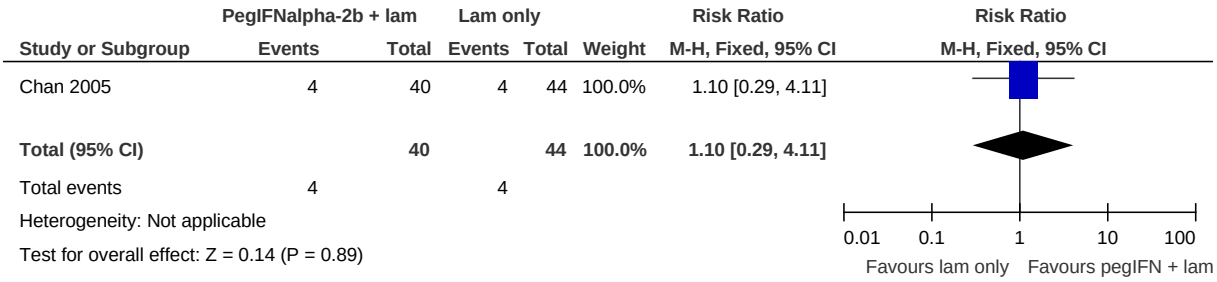


Figure 235: HBeAg loss at end treatment.

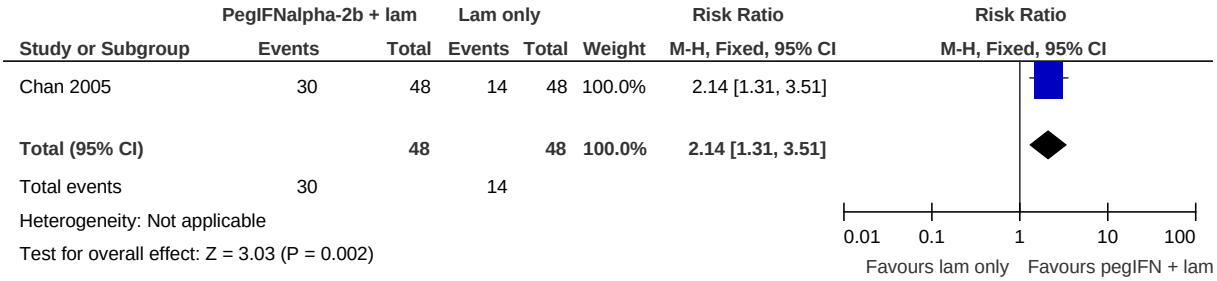


Figure 236: HBeAg seroconversion at end treatment.

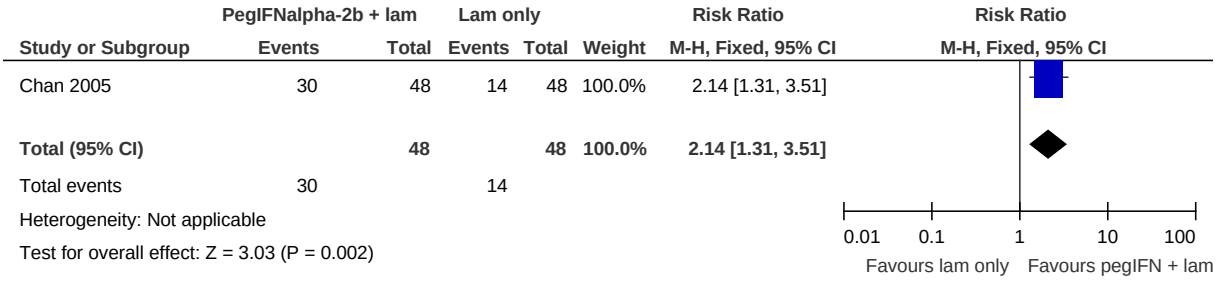


Figure 237: HBsAg loss at end treatment

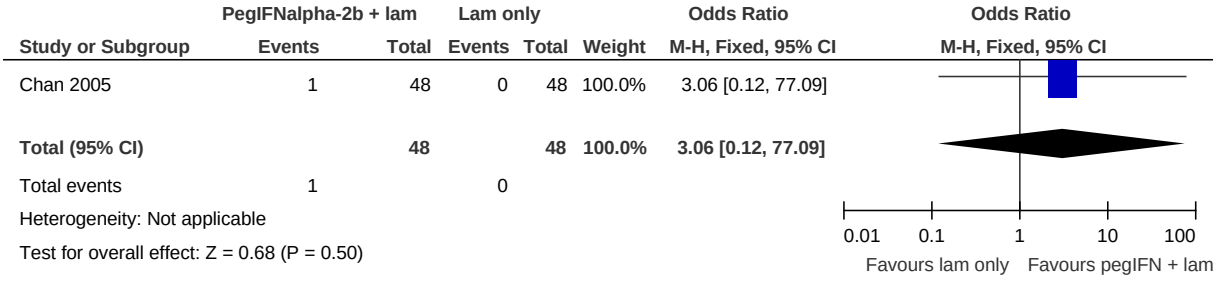


Figure 238: HBV DNA <100 copies/mL at 24 weeks follow up.

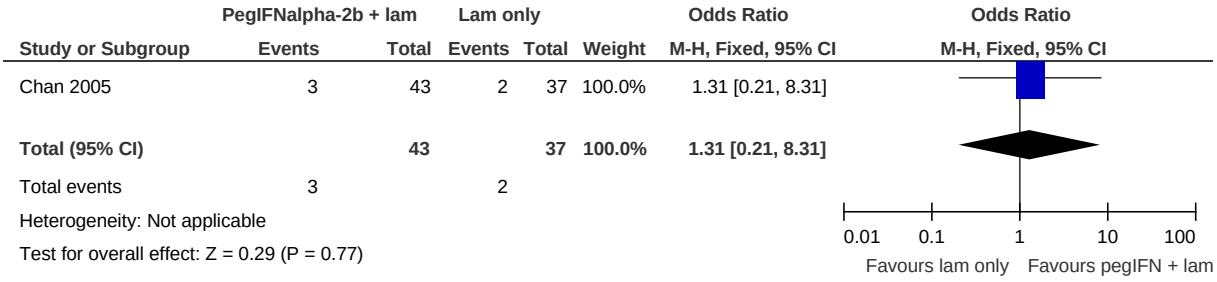
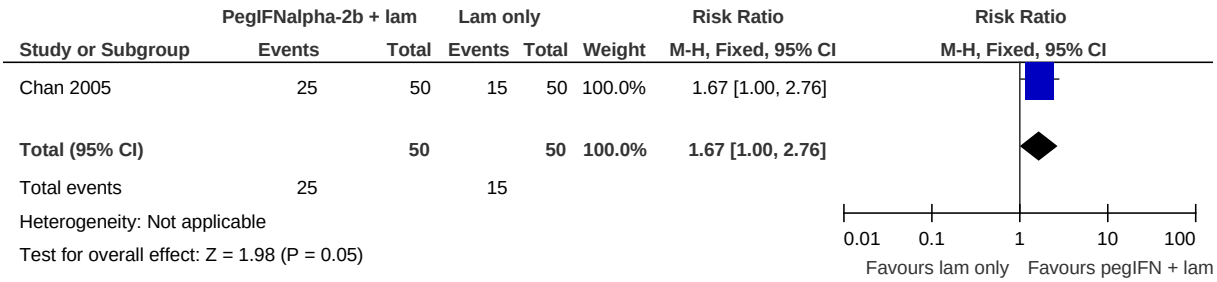


Figure 239: ALT normalisation at 24 weeks follow up.



G.3.1.2 Lamivudine resistant adults with HBeAg positive (or mixed) CHB

Comparison of entecavir versus placebo (mixed population: HBeAg positive and negative and lamivudine-resistant)

Figure 240: Mean reduction of HBV DNA from baseline (log_{10} copies/mL) (assessed at the end of 12 weeks treatment)

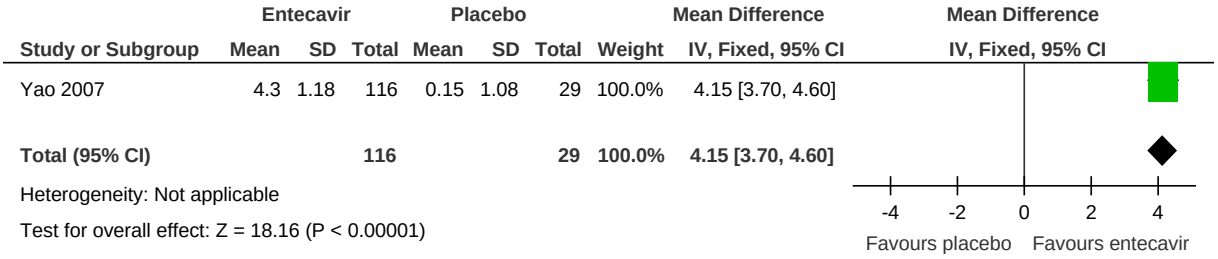


Figure 241: % of people with undetectable HBV DNA (assessed at the end of 12 weeks treatment)

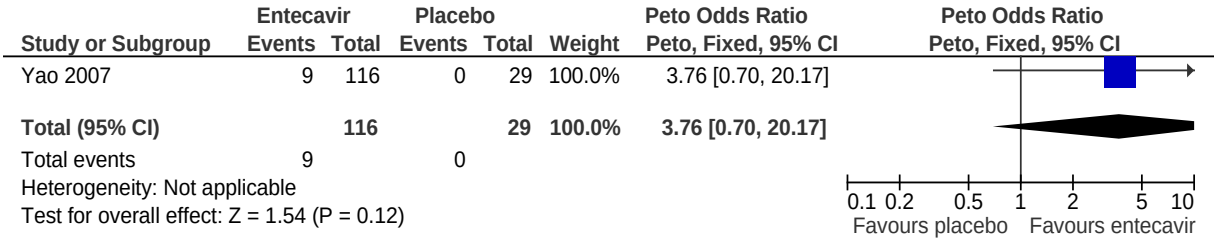


Figure 242: % of people with ALT normalisation (assessed at the end of 12 weeks treatment)

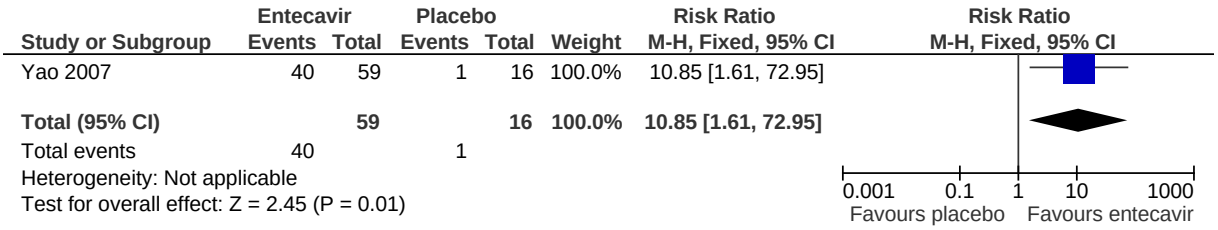
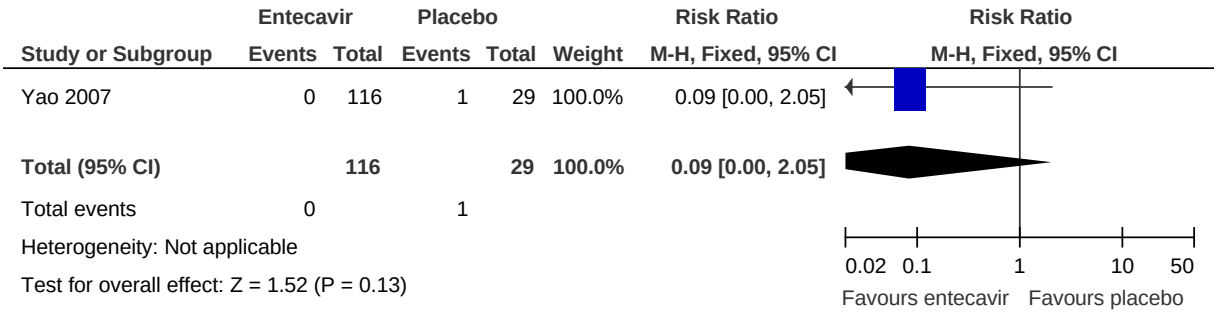


Figure 243: Adverse events leading to withdrawal.



Adefovir + lamivudine vs lamivudine (lamivudine resistant)

Figure 244: Undetectable HBV DNA at end of treatment.

Study or Subgroup	Lam + adefovir Events	Total	Lamivudine Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Perrillo 2004	9	42	0	46	58.2%	10.05 [2.55, 39.65]
Peters 2004	7	20	0	18	41.8%	9.66 [1.91, 48.84]
Total (95% CI)		**62**		**64**	**100.0%**	**9.88 [3.47, 28.17]**
Total events	16		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%

Test for overall effect: Z = 4.29 (P < 0.0001)

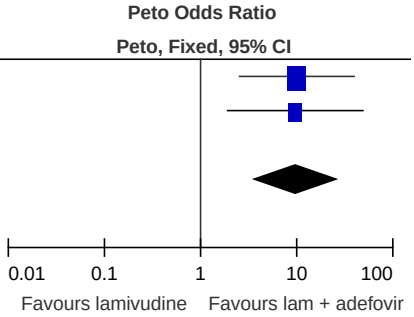


Figure 245: ALT normalisation at end of treatment.

Study or Subgroup	Lam + adefovir Events	Total	Lamivudine Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Perrillo 2004	14	42	3	46	80.1%	7.17 [1.89, 27.22]
Peters 2004	10	19	1	19	19.9%	20.00 [2.20, 181.56]
Total (95% CI)		**61**		**65**	**100.0%**	**9.72 [3.15, 30.02]**
Total events	24		4			

Heterogeneity: Chi² = 0.61, df = 1 (P = 0.43); I² = 0%

Test for overall effect: Z = 3.95 (P < 0.0001)

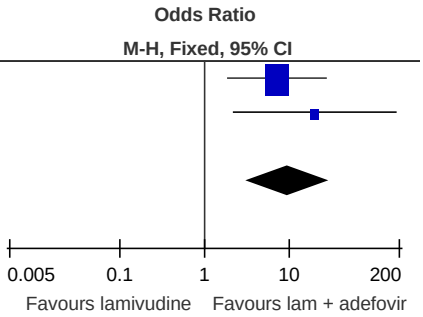


Figure 246: HBeAg loss at end of treatment.

Study or Subgroup	Lam + adefovir Events	Total	Lamivudine Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Perrillo 2004	6	40	1	42	67.6%	7.24 [0.83, 63.07]
Peters 2004	3	18	0	19	32.4%	8.81 [0.42, 183.61]
Total (95% CI)		**58**		**61**	**100.0%**	**7.74 [1.33, 45.11]**
Total events	9		1			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%

Test for overall effect: Z = 2.28 (P = 0.02)

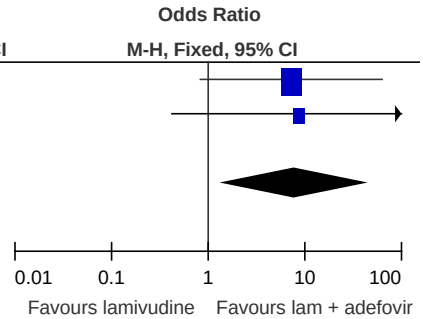


Figure 247: HBeAg seroconversion at end of treatment.

Study or Subgroup	Lam + adefovir Events	Total	Lamivudine Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Perrillo 2004	3	40	1	42	66.8%	3.32 [0.33, 33.37]
Peters 2004	1	18	0	19	33.2%	3.34 [0.13, 87.52]
Total (95% CI)		**58**		**61**	**100.0%**	**3.33 [0.51, 21.91]**
Total events	4		1			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 1.25 (P = 0.21)

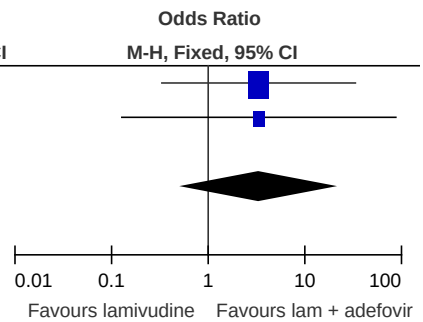
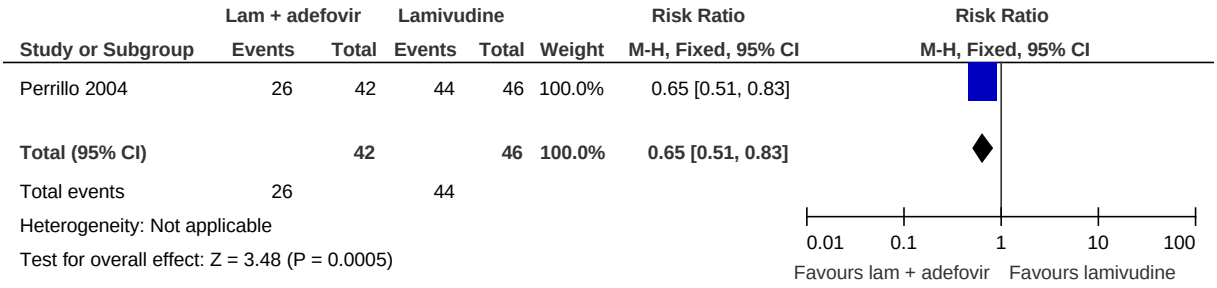


Figure 248: Resistance at end of treatment.



ADF + LAM v ADF (lamivudine resistant)

Figure 249: reduction in HBV DNA (end of 48 weeks treatment

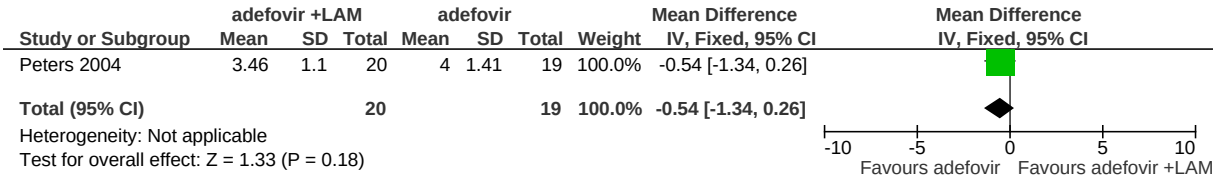


Figure 250: Undetectable HBV DNA (<1000 copies/ml) (end of 48 weeks treatment)

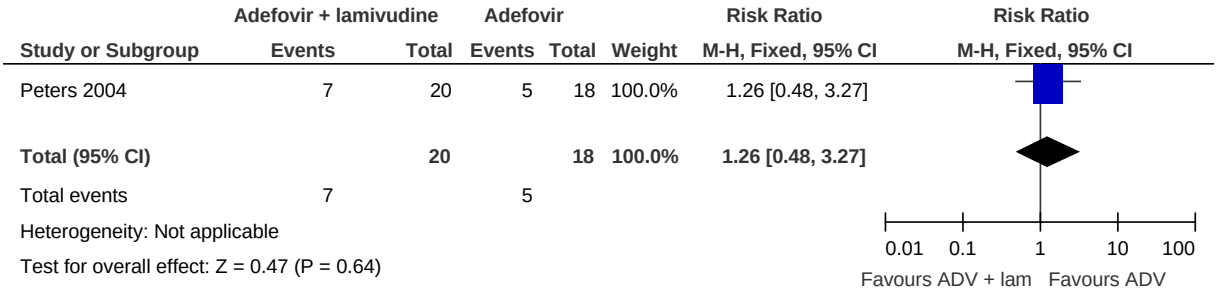


Figure 251: HBeAg loss end of treatment.

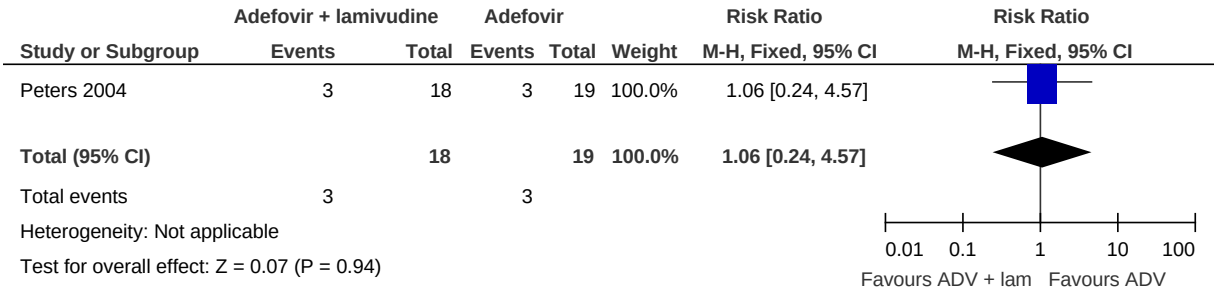


Figure...HBeAg seroconversion (end of 48 weeks treatment)

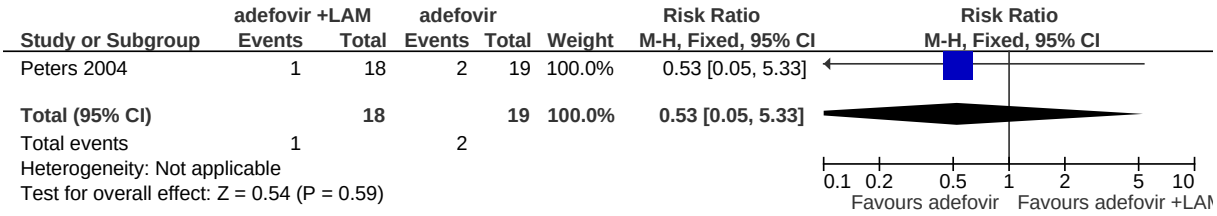
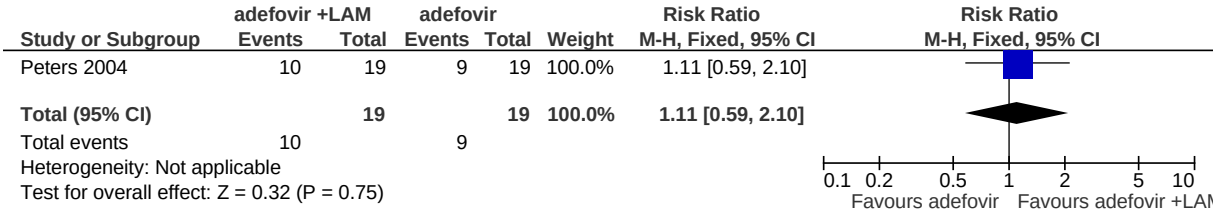


Figure 252: ALT normalization (end of 48 weeks treatment)



ADF vs. LAM (lamivudine resistant

Figure 253: Undetectable HBV DNA at end of treatment.

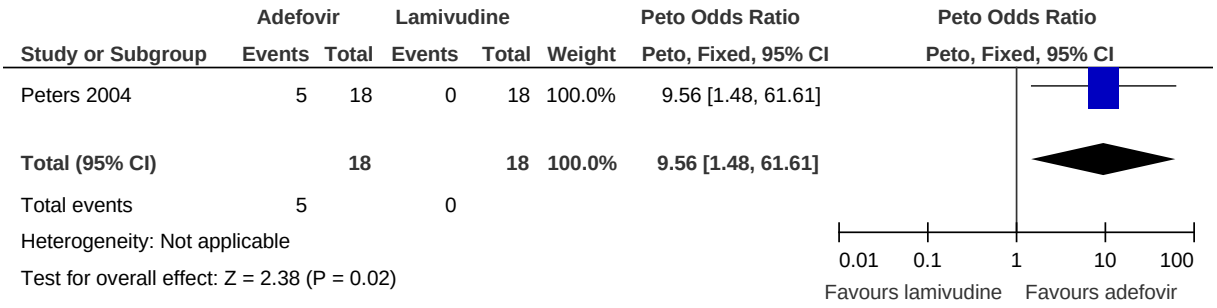


Figure 254: ALT normalisation at end of treatment.

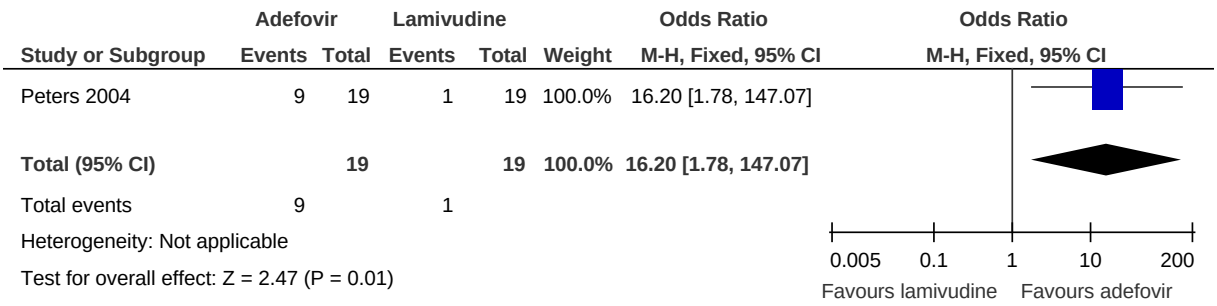


Figure 255: HBeAg loss at end of treatment.

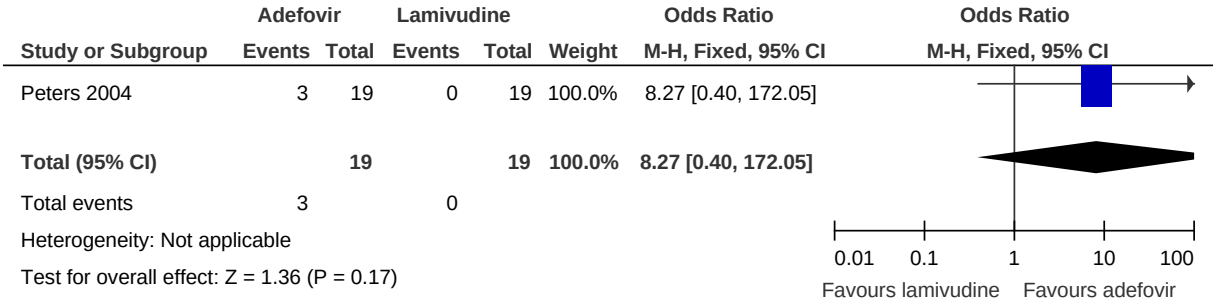
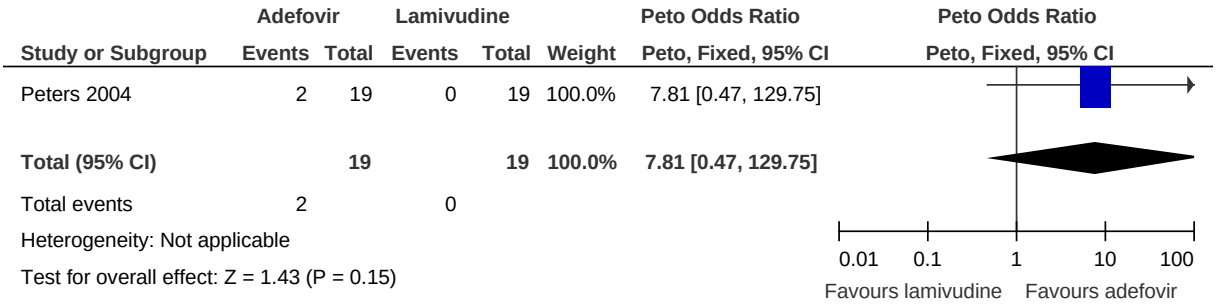
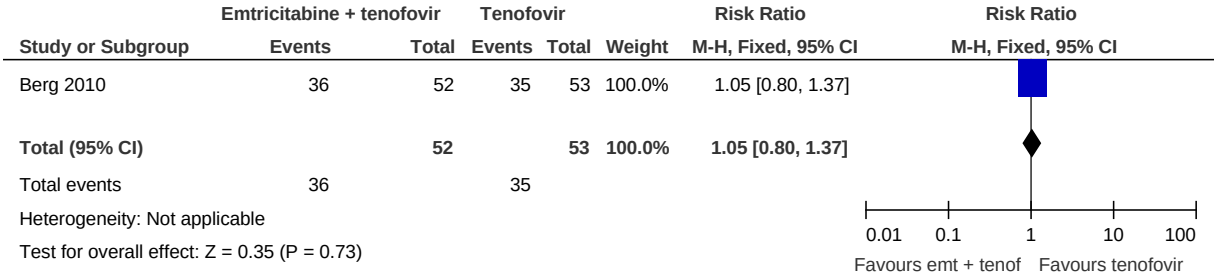


Figure 256: HBeAg seroconversion at end of treatment.



EMTRICITABINE + TDF v TDF

Figure 257: HBV DNA <400 copies/mL at 24 weeks of therapy.



G.3.1.3 Pharmacological monotherapy and combination therapies in achieving remission of the action of CHB infection for HBeAg negative adults

Comparison of adefovir versus placebo (HBeAg negative)

Figure 258: % of people with undetectable HBV DNA (<400 copies/ml)

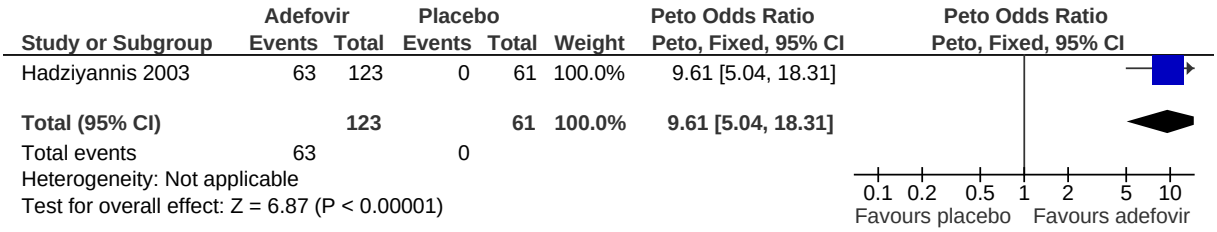


Figure 259: % of people with ALT normalisation

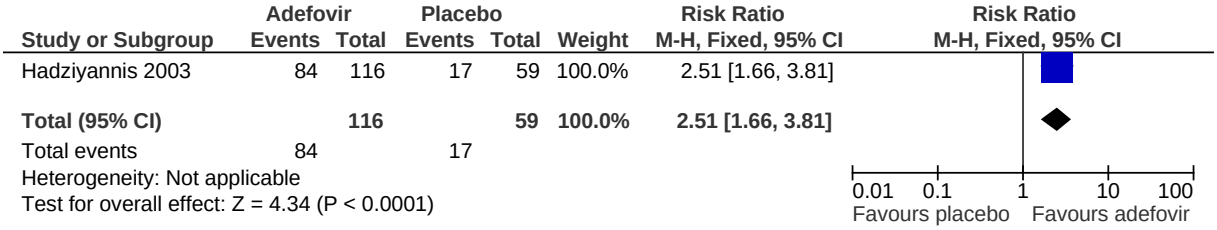
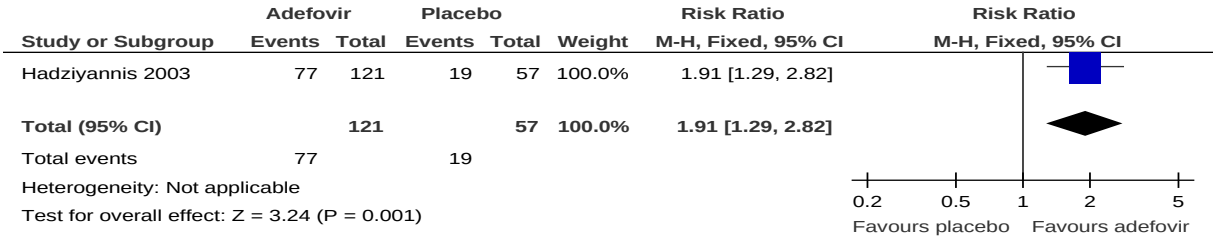
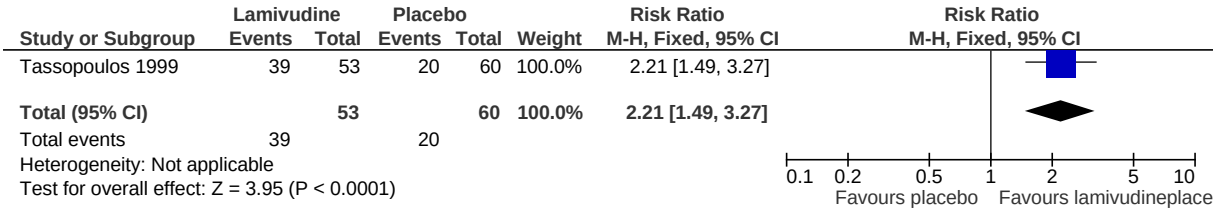


Figure 260: % of people with histologic improvement



Comparison of lamivudine versus placebo (HBeAg negative)

Figure 261: % of people with undetectable DNA (<2.5pg/ml) (end of 24 weeks treatment)



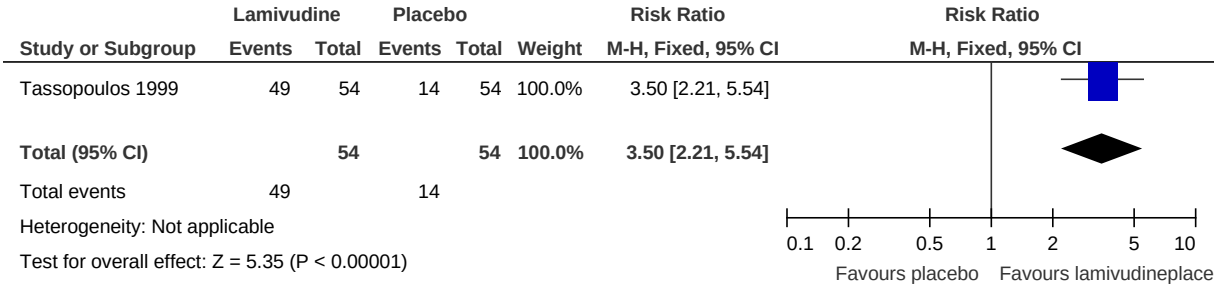
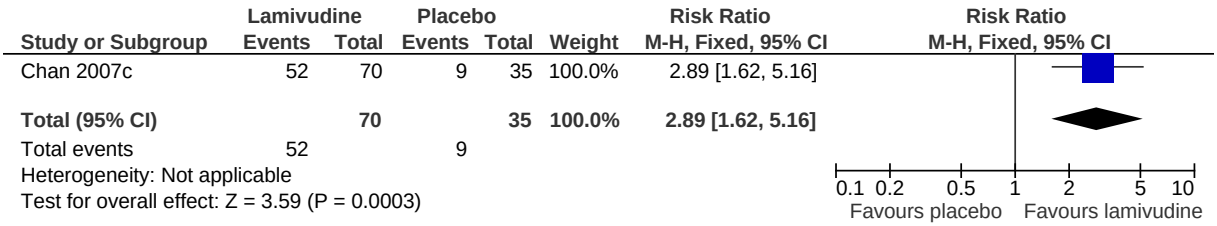


Figure 262: % of people with undetectable HBV DNA (<10,000 copies/ml) (assessed at the end of 24 months treatment)



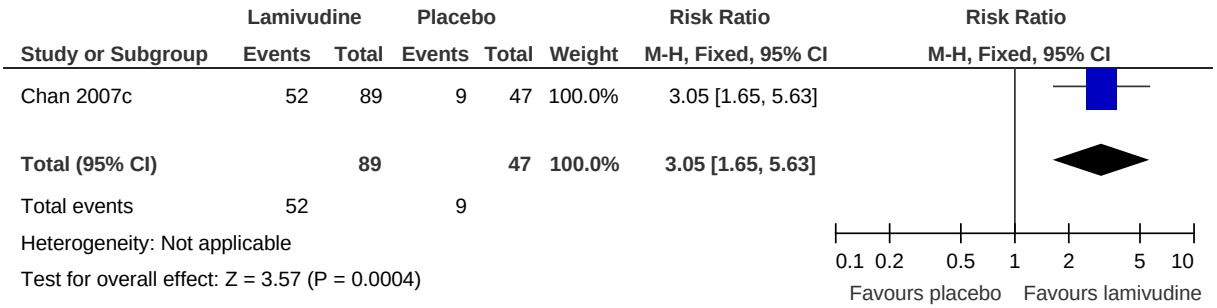
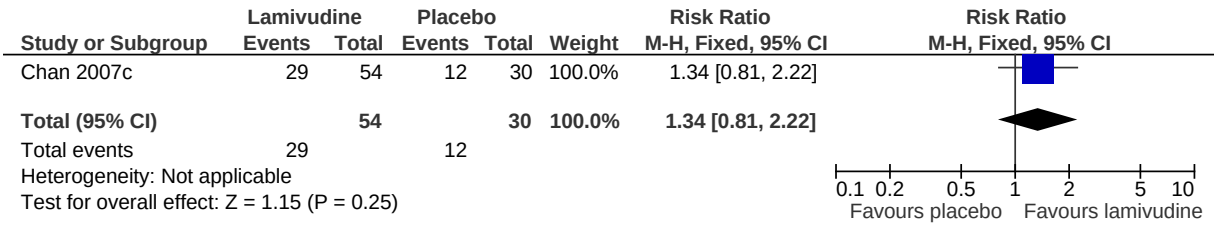


Figure 263: % of people with undetectable HBV DNA (<10,000copies/ml) (assessed at 6 months follow up)



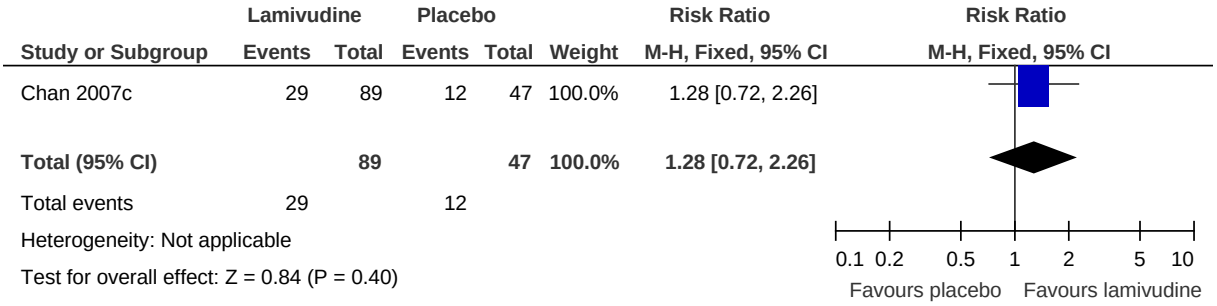
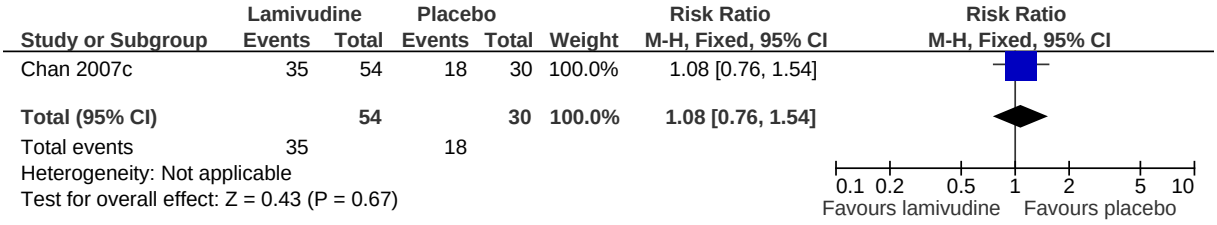


Figure 264: % of people with ALT normalisation (assessed at the end of 24 months treatment)



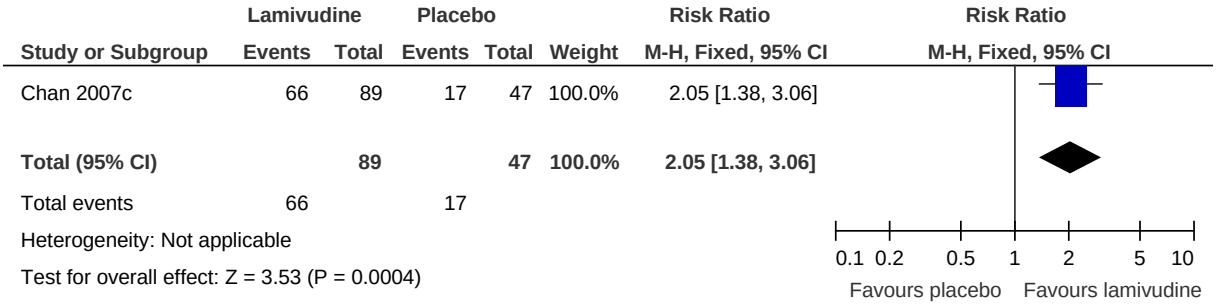
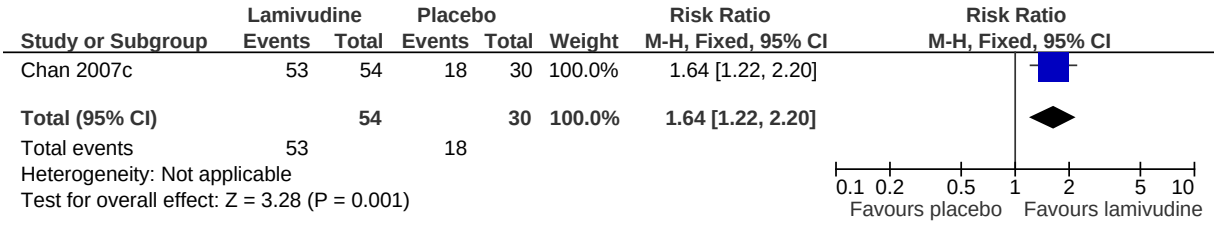


Figure 265: % of people with ALT normalisation (assessed at 6 months follow up)



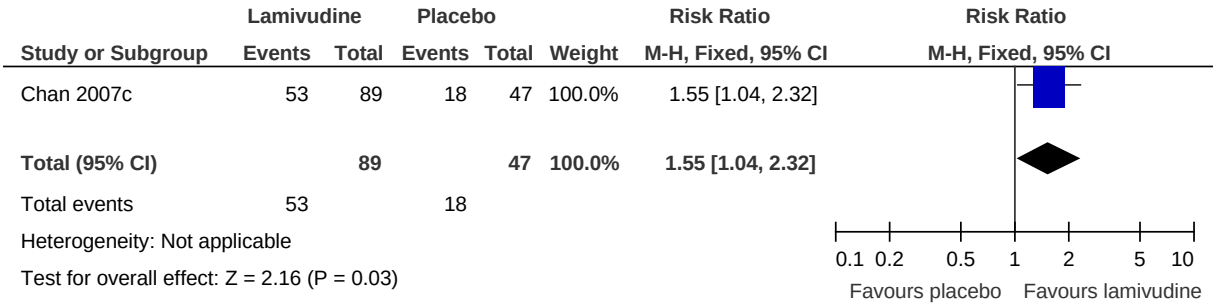
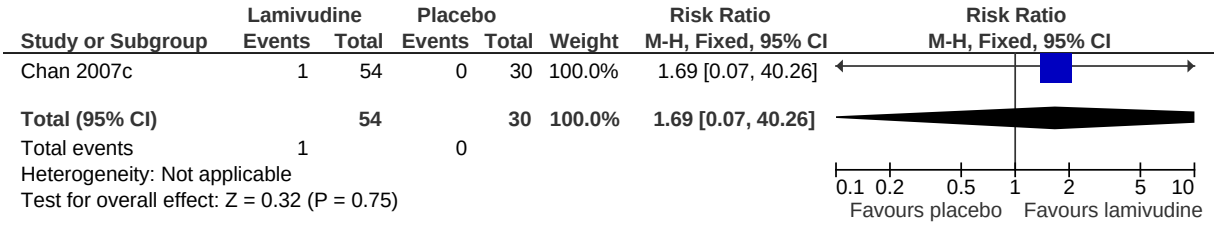


Figure 266: % of people with HBsAg loss (end of treatment or 6 months after).

(assessed at 6 months follow up)



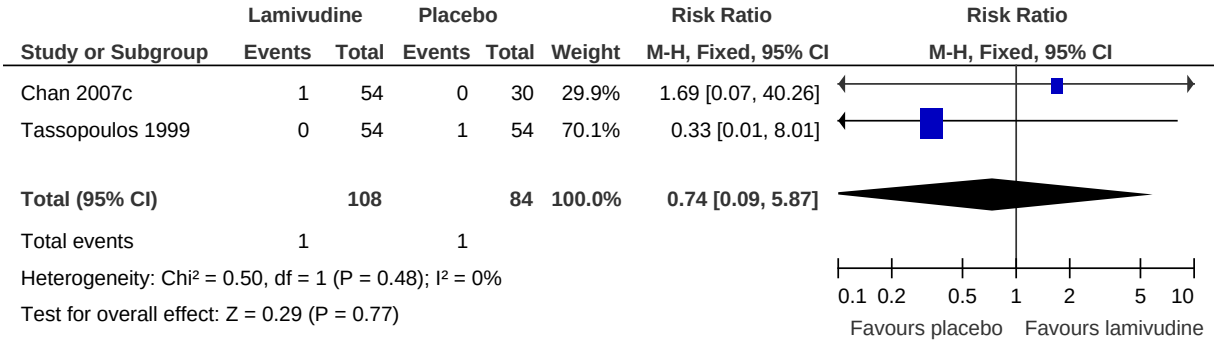


Figure 267:

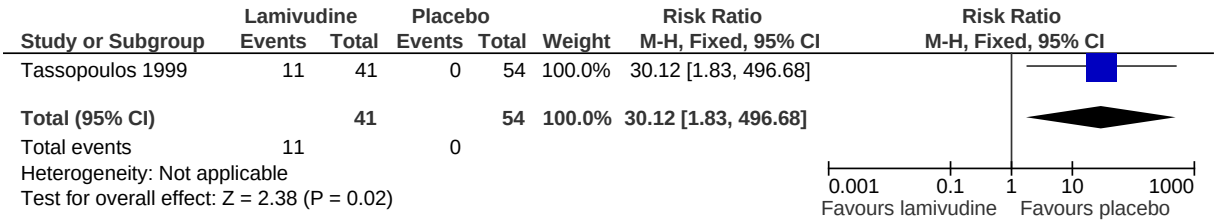
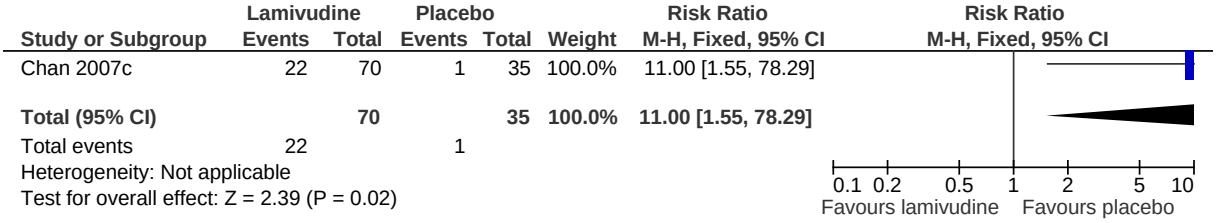


Figure 268: Incidence of resistance (genotypic mutation) (end of 24 months)



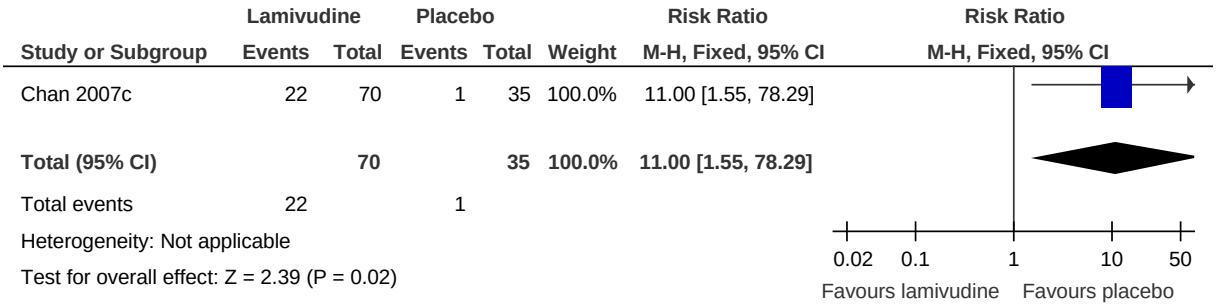
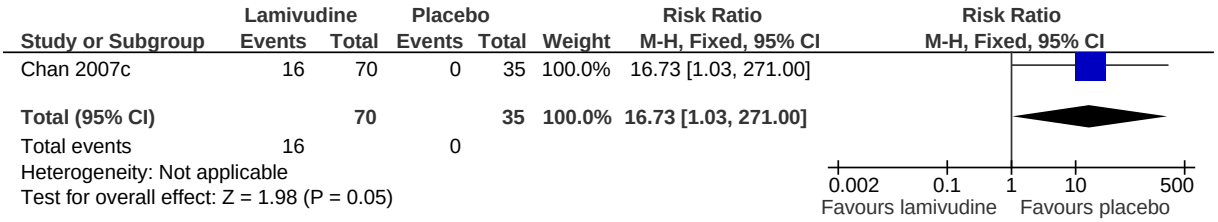


Figure 269: Incidence of resistance (viral breakthrough) (end of 24 months)



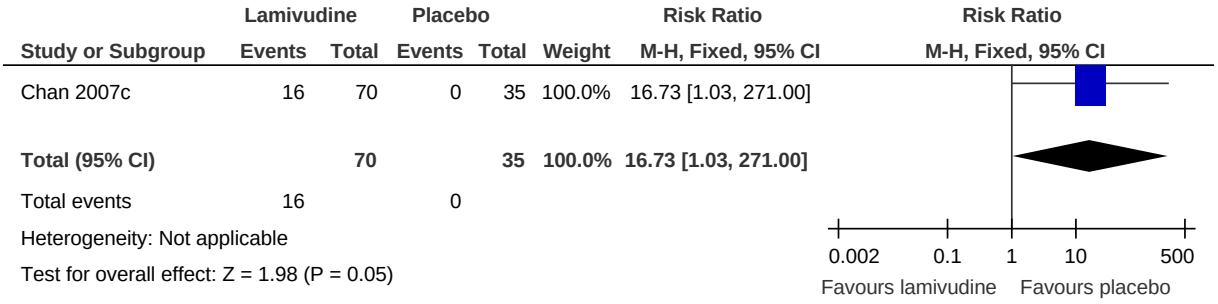
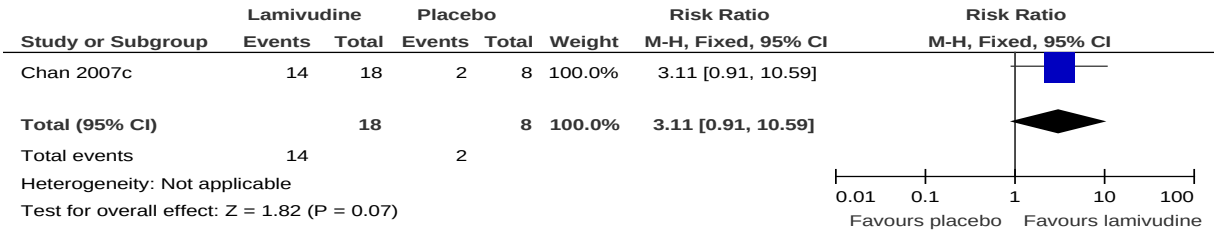
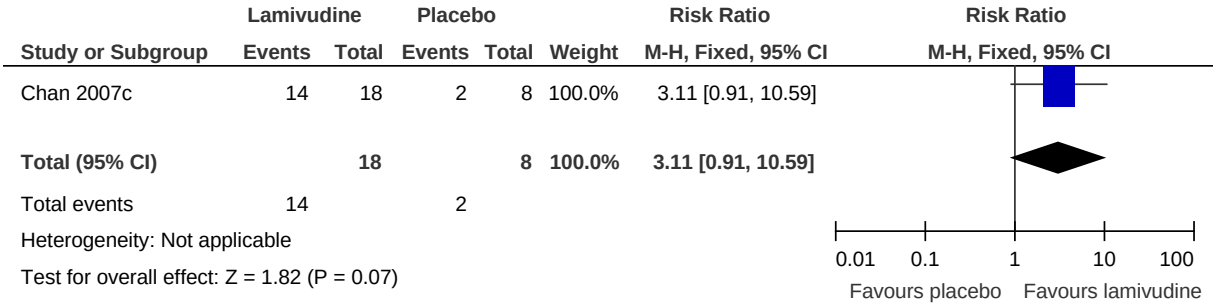


Figure 270: % of people with Histologic improvement (end of 24 months)





Comparison of lamivudine versus pegylated interferon-alpha 2a (HBeAg negative) Marcellin 2004

Figure 271: Mean reduction of HBV DNA (end of 48 week treatment)

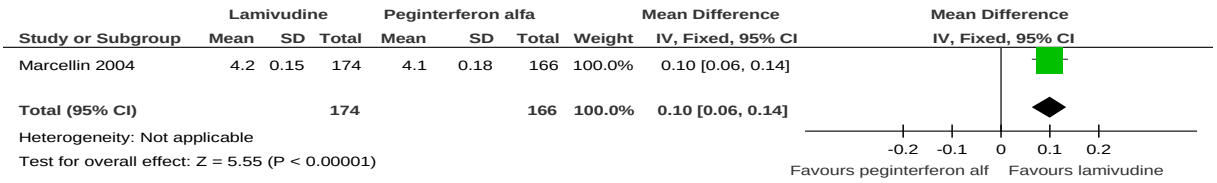


Figure 272: Mean reduction of HBV DNA (end of 24 week follow up)

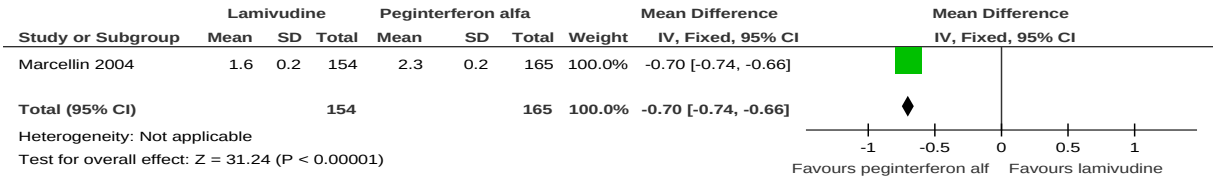


Figure 273: % of people with undetectable HBV DNA (end of 48 week treatment)

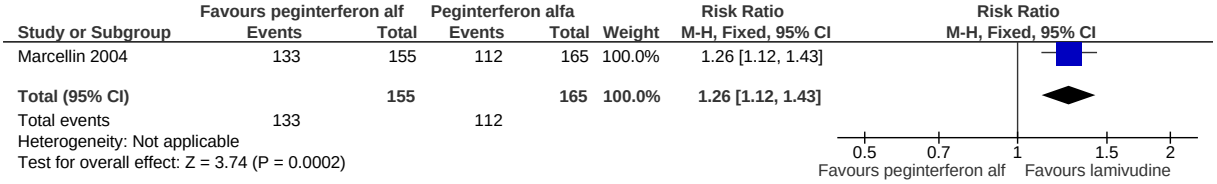


Figure 274: % of people with undetectable HBV DNA (end of 24 week follow up)

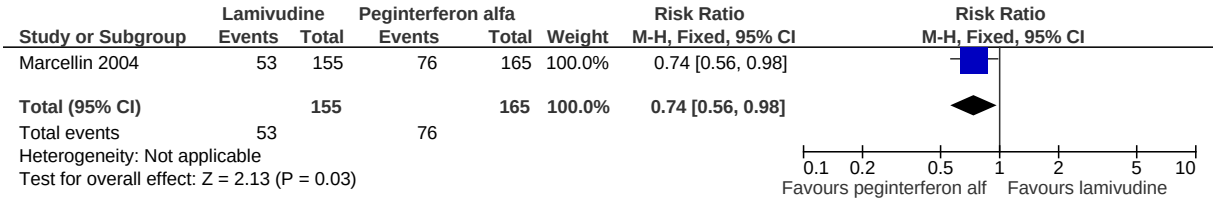


Figure 275: % of people with HBsAg loss (end of 24 week follow up)

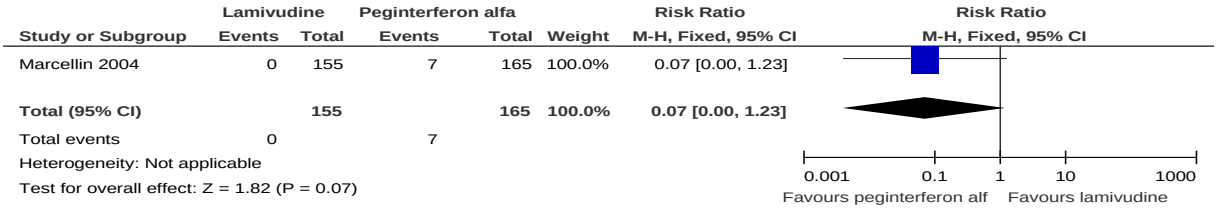


Figure 276: % of people with HBsAg seroconversion (end of 24 week follow up)

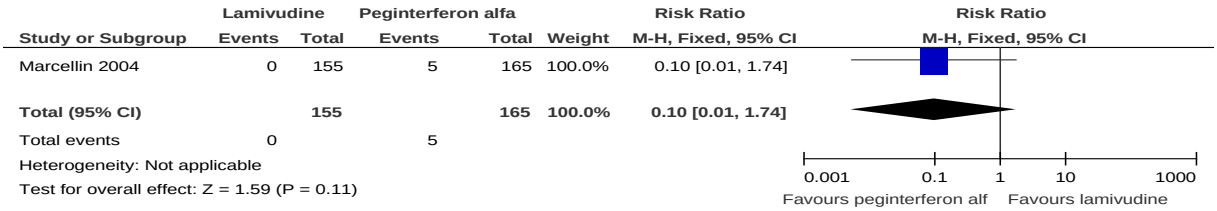


Figure 277: % of people with ALT normalisation (end of 48 week treatment)

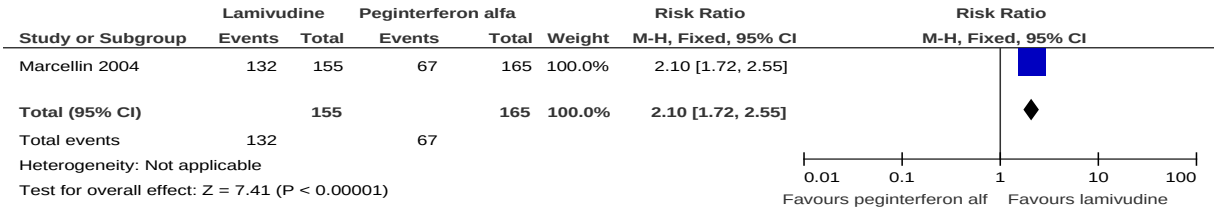


Figure 278: % of people with ALT normalisation (end of 24 week follow up)

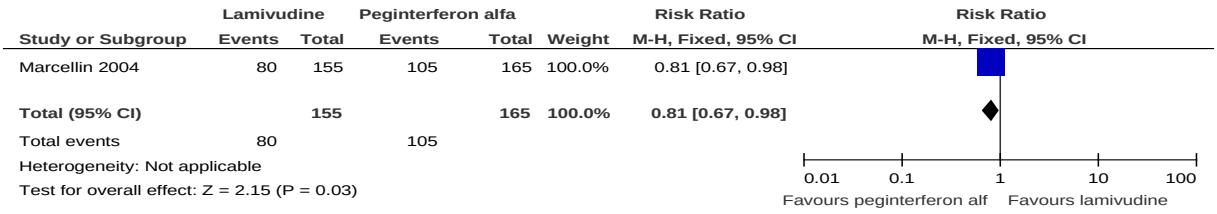


Figure 279: Incidence of resistance – genotypic mutation (assessed at 48 week treatment)

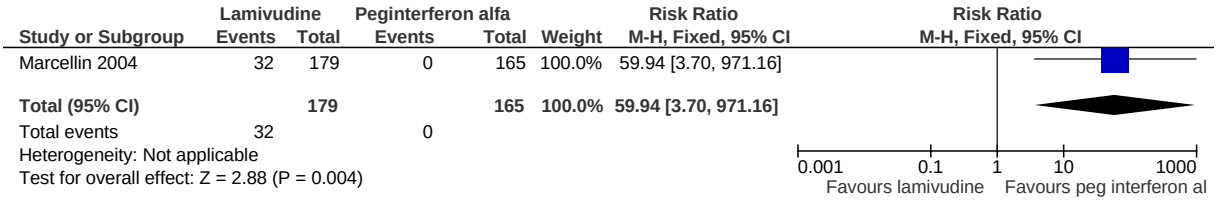
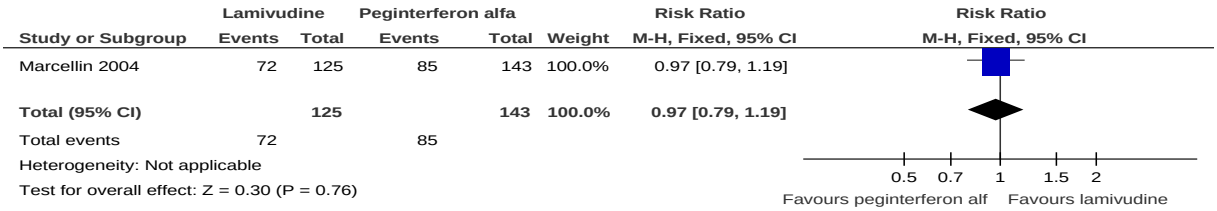


Figure 280: % of people with Histologic improvement (end of 24 week follow up)



Comparison of telbivudine versus lamivudine (HBeAg negative people)

Figure 281: Mean reduction of HBV DNA

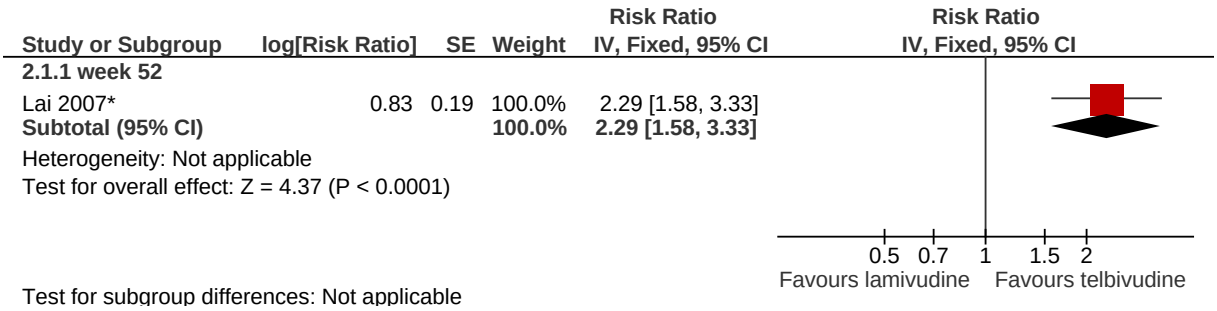


Figure 282: % of people with undetectable HBV DNA

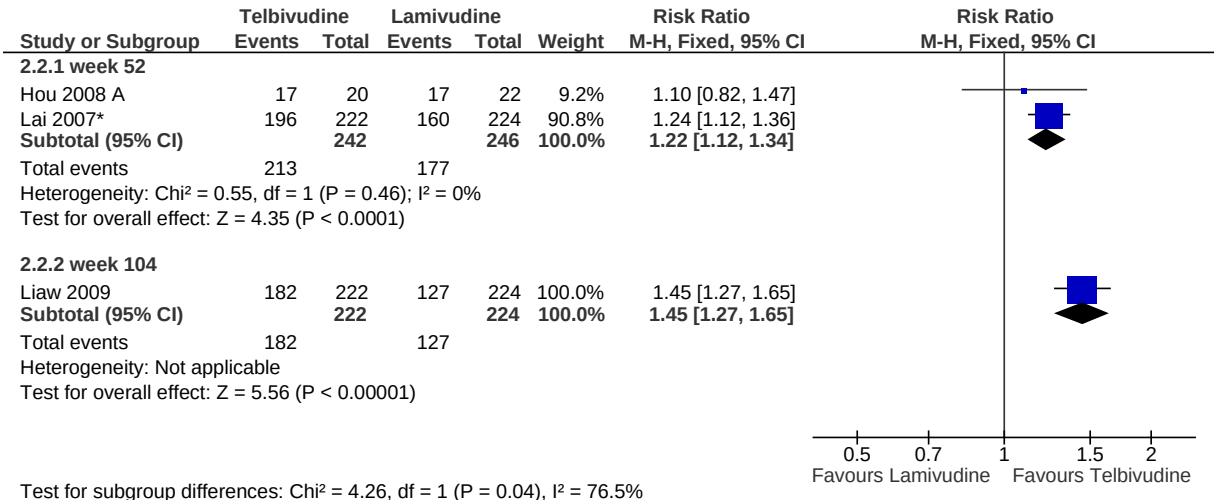


Figure 283: % of people with ALT normalisation

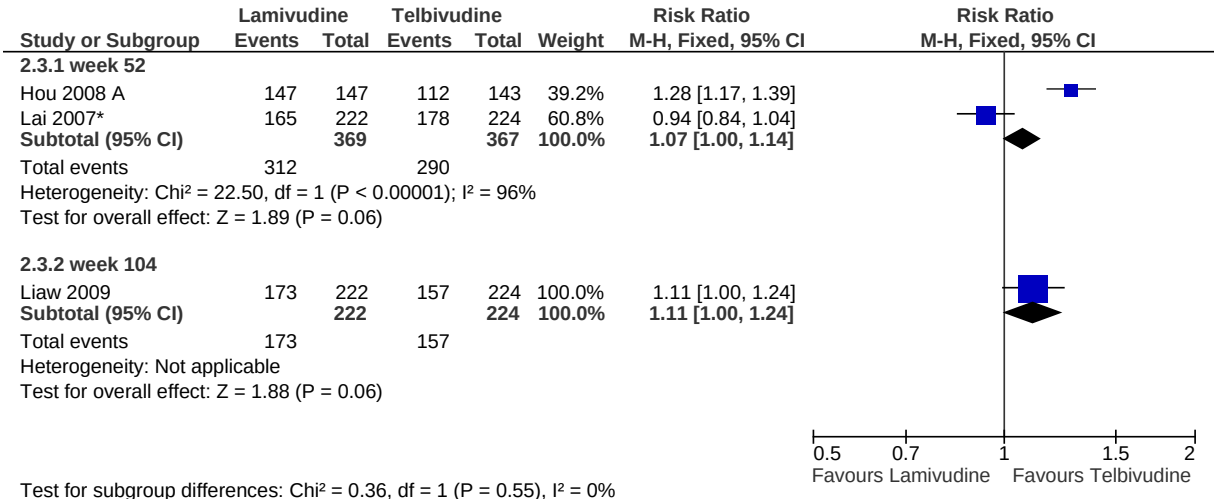


Figure 284: % of people with HBsAg loss (week 104)

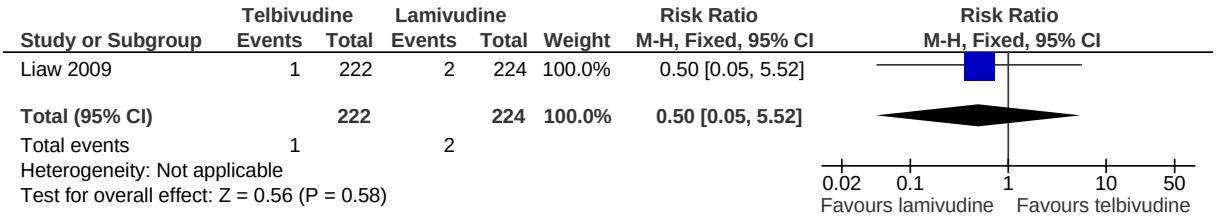


Figure 285: % of people with HBsAg seroconversion (assessed at week 104)

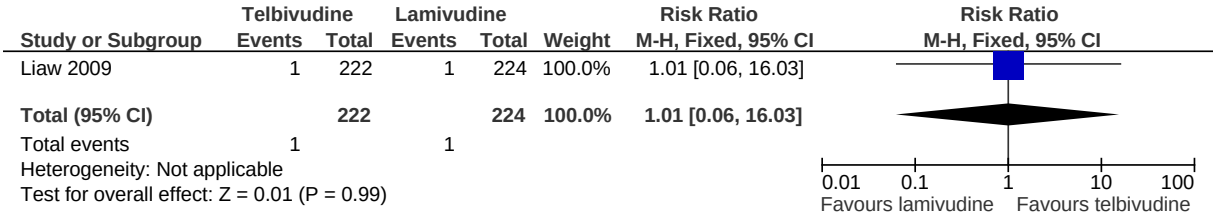


Figure 286: Incidence of resistance (viral breakthrough accompanied by genotypic mutation)

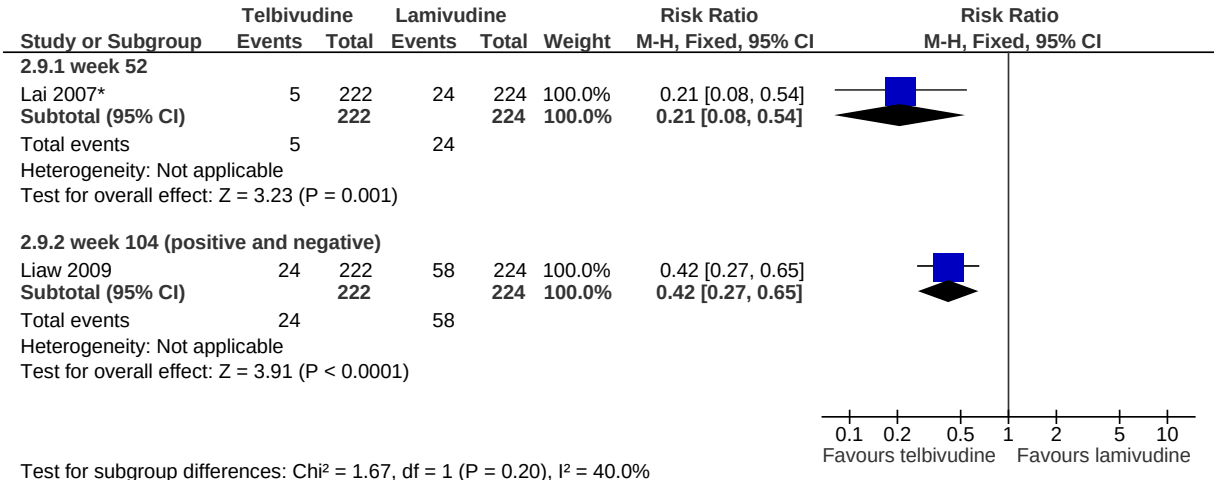
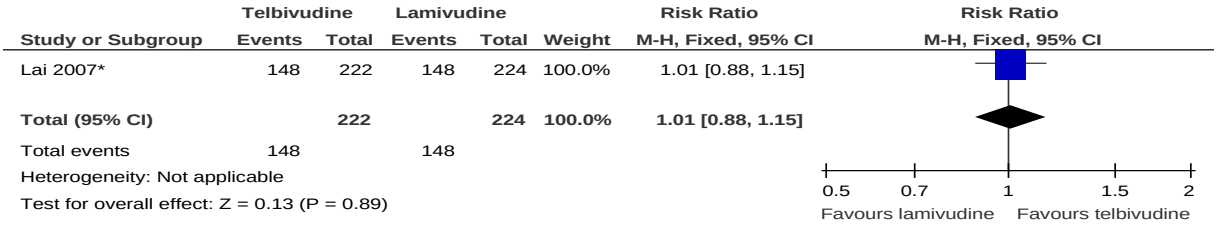


Figure 287: % of people with Histologic improvement



Comparison of tenofovir versus adefovir (HBeAg negative)

Figure 288: mean reduction of HBV DNA

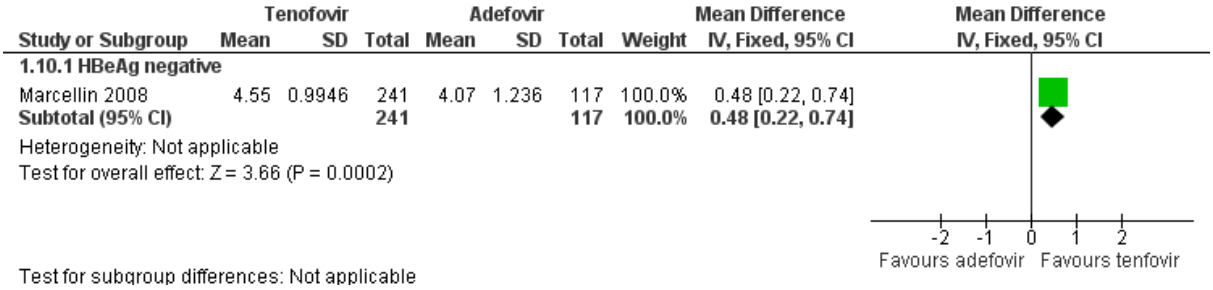


Figure 289: % of people with HBV DNA <400copies/mL

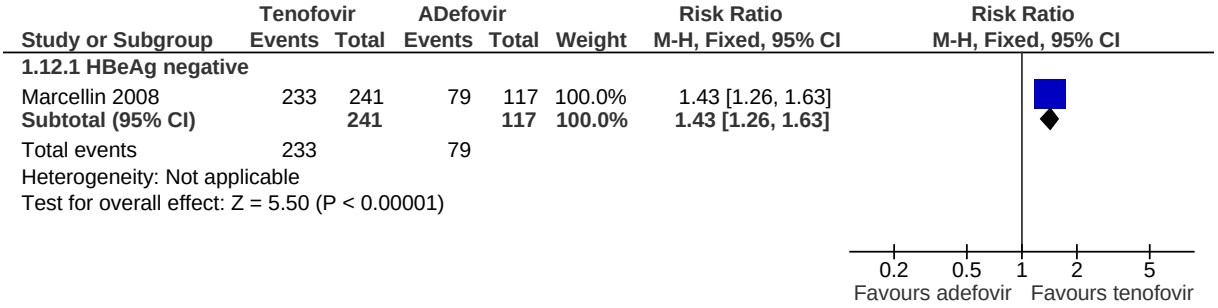


Figure 290: % of people with HBsAg loss

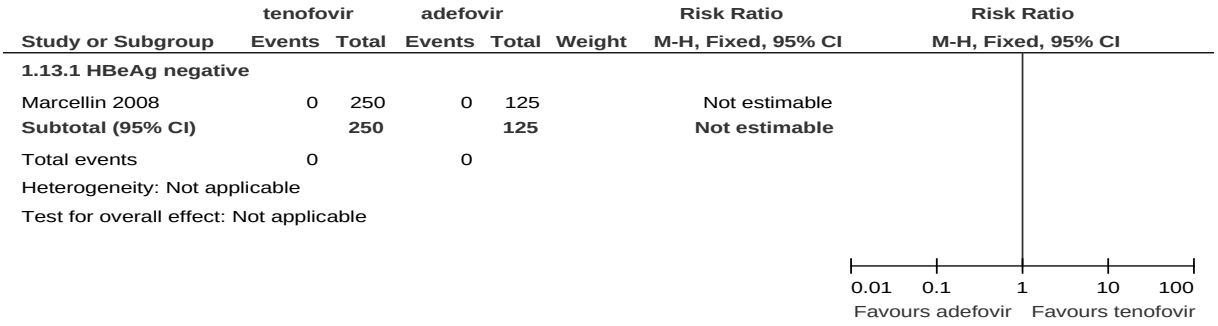


Figure 291: % of people with ALT normalisation

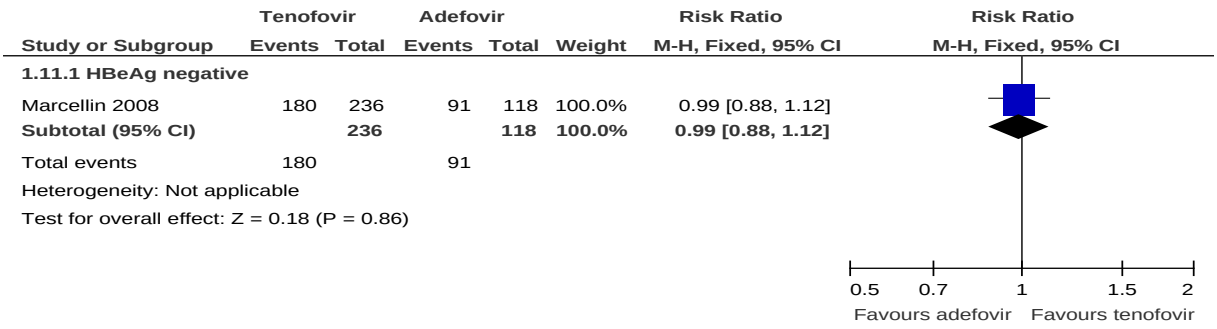
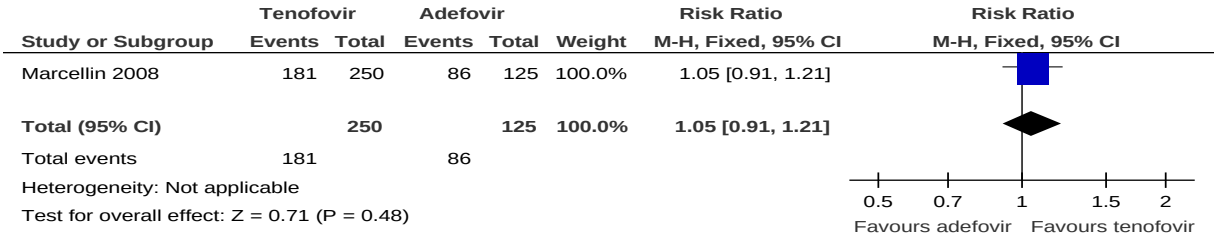


Figure 292: % of people with histologic improvement



ADD forest plots for Economou 2005, Santantonio 2002, Akarca 2004 and Yurdaydin 2005 and Piccolo 2008 (GRADE tables are already in the report).

Comparison of entecavir versus lamivudine (HBeAg negative people)

Figure 293: Log reduction in HBV DNA (end of treatment – week 48)

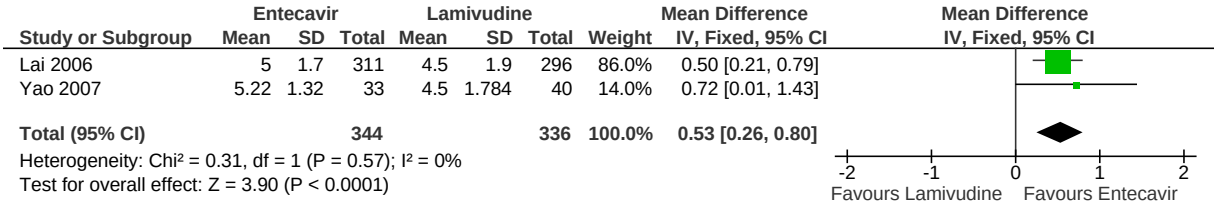


Figure 294: % of people with undetectable HBV DNA (<300 copies/mL – week 48)

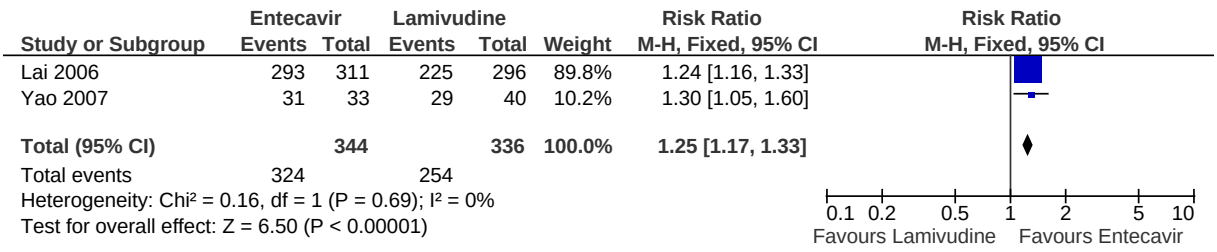


Figure 295: % of people with undetectable HBV DNA (<0.7 MEq/mL – week 48)

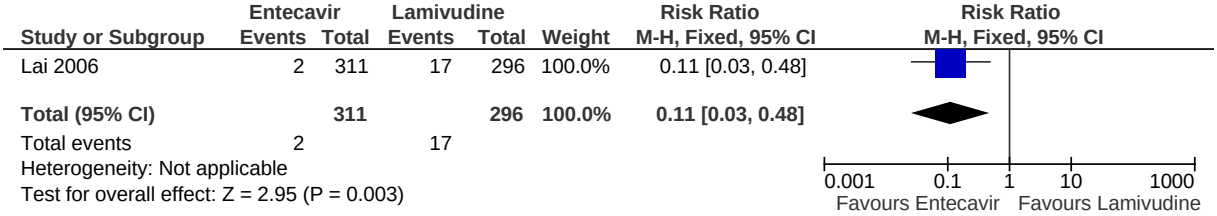


Figure 296: Normalisation of serum ALT (end of treatment – week 48)

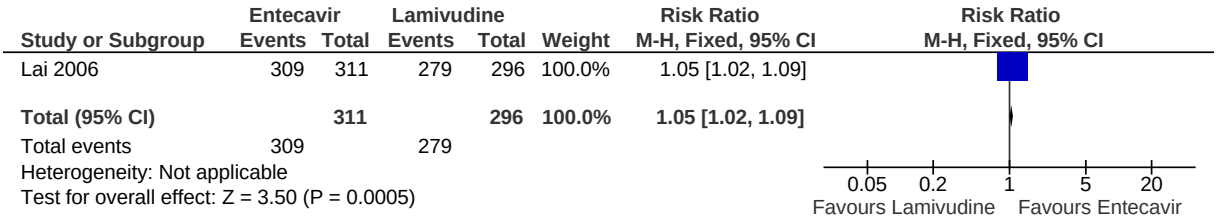


Figure 297: Incidence of resistance - viral breakthrough (assessed at week 48)

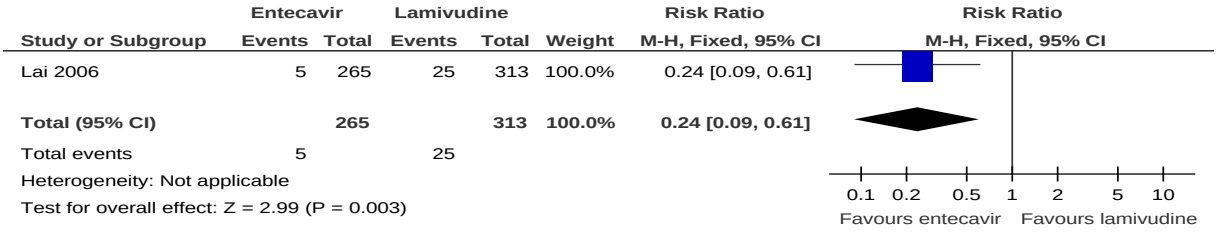
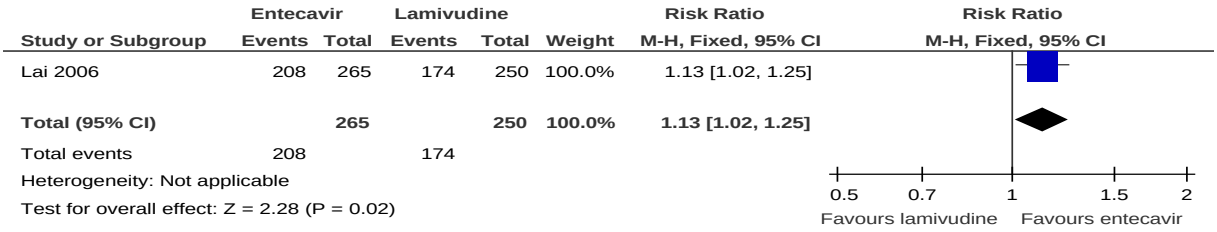


Figure 298: % of people with Histologic improvement



Pega2a + LAM v Pega2a (HBeAg negative) Marcellin 2004

Figure 299: HBV DNA log reduction (copies/ml) (end of 48 week treatment)

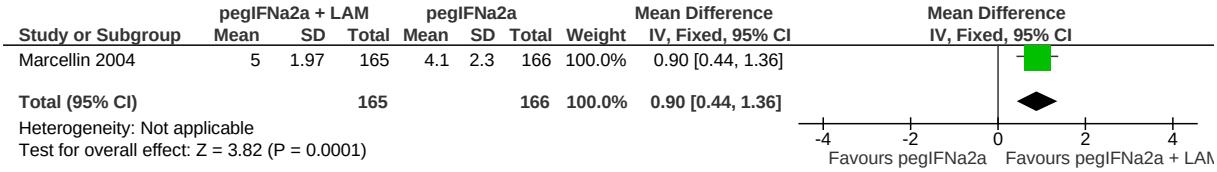


Figure 300: % of patients with detectable HBV DNA (> 20,000 copies/ml(end of 48 week treatment))

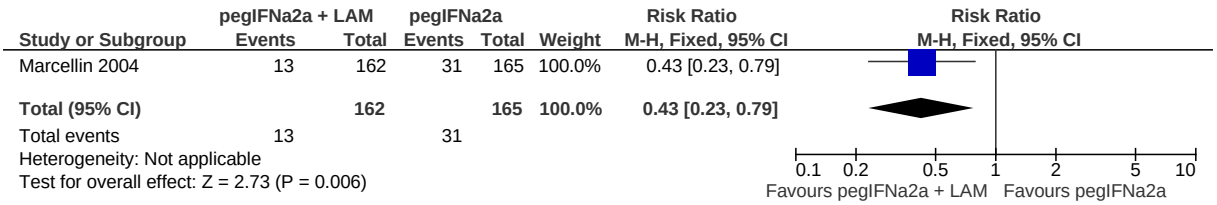


Figure 301: ALT normalization (end of 48 week treatment)

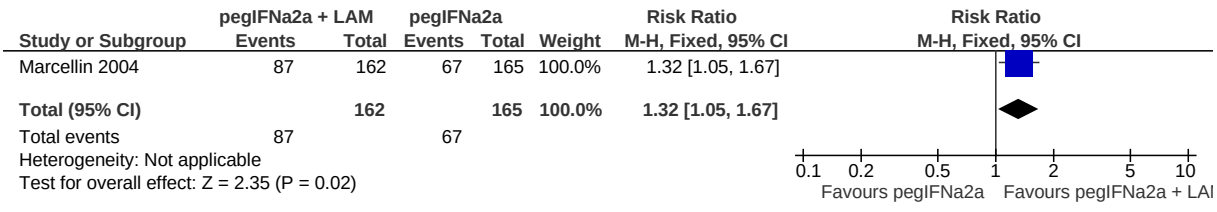


Figure 302: HBV DNA log reduction (copies/ml) (end of 24 week follow up)

Study or Subgroup	pegIFNa2a + LAM Mean	SD	Total	pegIFNa2a Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Marcellin 2004	2.4	2.99	170	2.3	2.62	165	100.0%	0.10 [-0.50, 0.70]
Total (95% CI)			**170**			**165**	**100.0%**	**0.10 [-0.50, 0.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

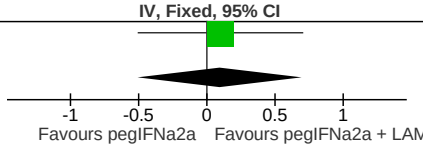


Figure 303: % of patients with detectable HBV DNA (> 20,000 copies/ml end of 24 week follow up)

Study or Subgroup	pegIFNa2a + LAM Events	Total	pegIFNa2a Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marcellin 2004	90	162	94	165	100.0%	0.98 [0.81, 1.18]
Total (95% CI)		**162**		**165**	**100.0%**	**0.98 [0.81, 1.18]**
Total events	90		94			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)

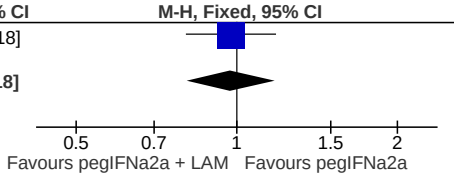


Figure 304: HBsAg loss (end of 24 week follow up)

Study or Subgroup	pegIFNa2a + LAM Events	Total	pegIFNa2a Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marcellin 2004	5	162	7	165	100.0%	0.73 [0.24, 2.25]
Total (95% CI)		**162**		**165**	**100.0%**	**0.73 [0.24, 2.25]**
Total events	5		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)

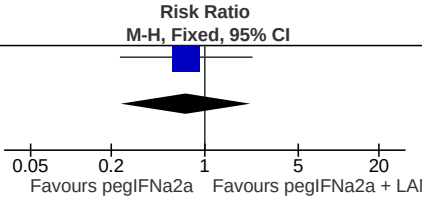


Figure 305: HBsAg seroconversion (end of 24 week follow up)

Study or Subgroup	pegIFNa2a + LAM Events	Total	pegIFNa2a Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marcellin 2004	3	162	5	165	100.0%	0.61 [0.15, 2.52]
Total (95% CI)		**162**		**165**	**100.0%**	**0.61 [0.15, 2.52]**
Total events	3		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)

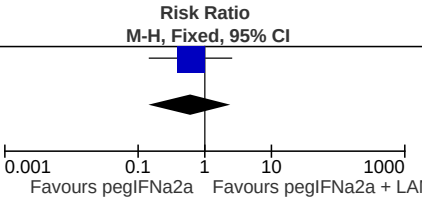


Figure 306: ALT normalization (end of 24 week follow up)

Study or Subgroup	pegIFNa2a + LAM Events	Total	pegIFNa2a Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marcellin 2004	107	162	105	165	100.0%	1.04 [0.88, 1.22]
Total (95% CI)		**162**		**165**	**100.0%**	**1.04 [0.88, 1.22]**
Total events	107		105			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

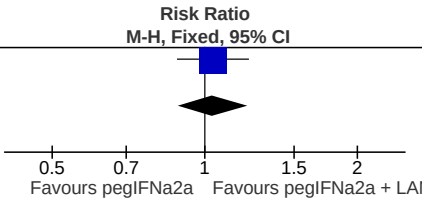


Figure 307: Histologic improvement (end of 24 week follow up)

Study or Subgroup	pegIFNa2a + LAM Events	Total	pegIFNa2a Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marcellin 2004	68	143	85	143	100.0%	0.80 [0.64, 1.00]
Total (95% CI)		**143**		**143**	**100.0%**	**0.80 [0.64, 1.00]**
Total events	68		85			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)

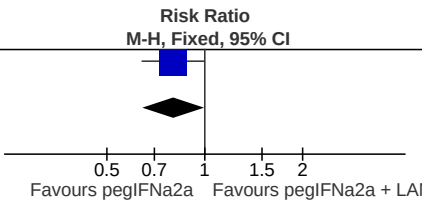
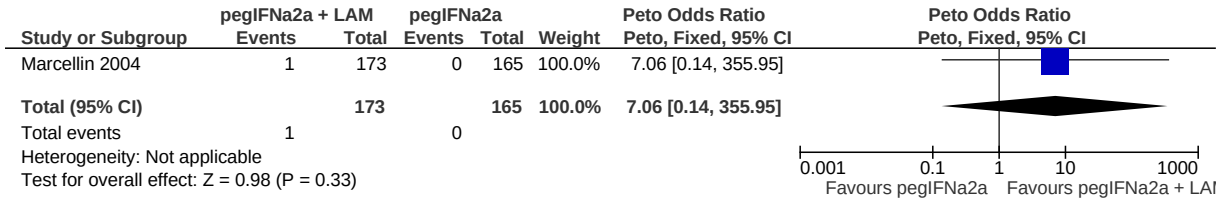


Figure 308: Resistance (genotypic mutation)



Pega2b + LAM v Pega2b (HBeAg negative)

Figure 309: Normalisation of ALT end of 48 weeks treatment.

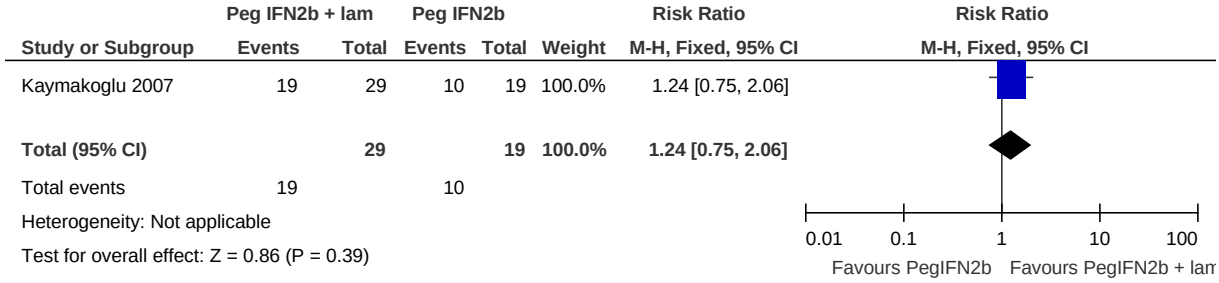


Figure 310: Normalisation of ALT after 24 weeks follow up.

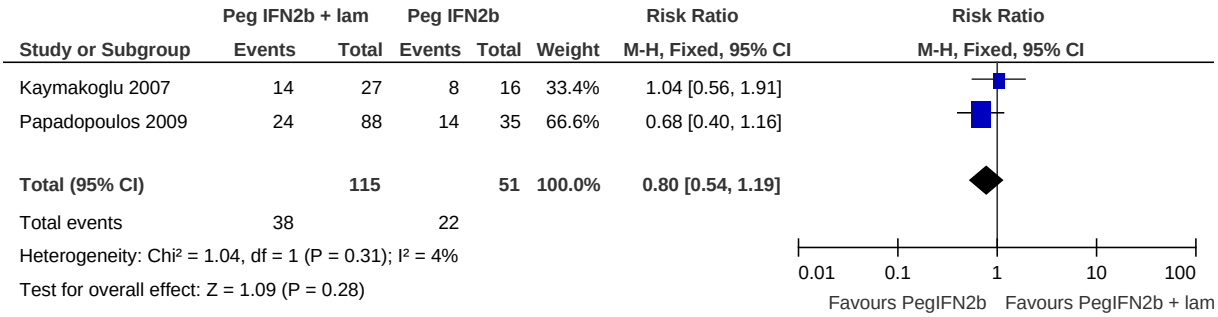


Figure 311: Undetectable HBV DNA at end of 48 weeks treatment.

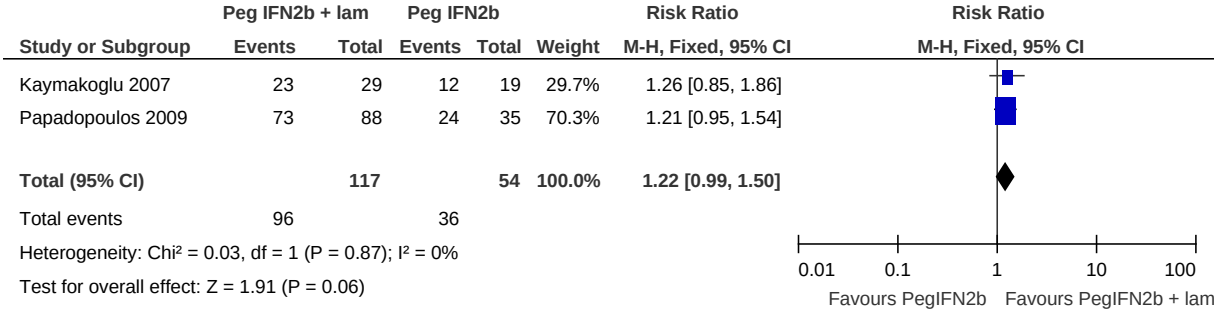


Figure 312: Undetectable HBV DNA at end of 48 weeks treatment.

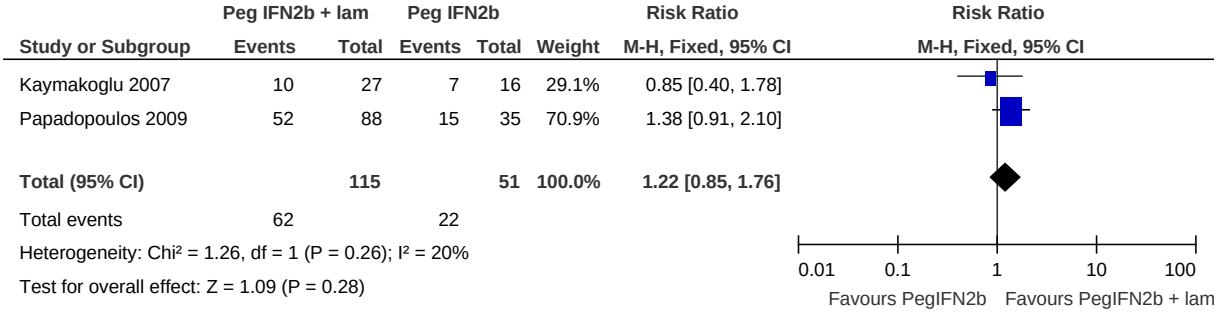
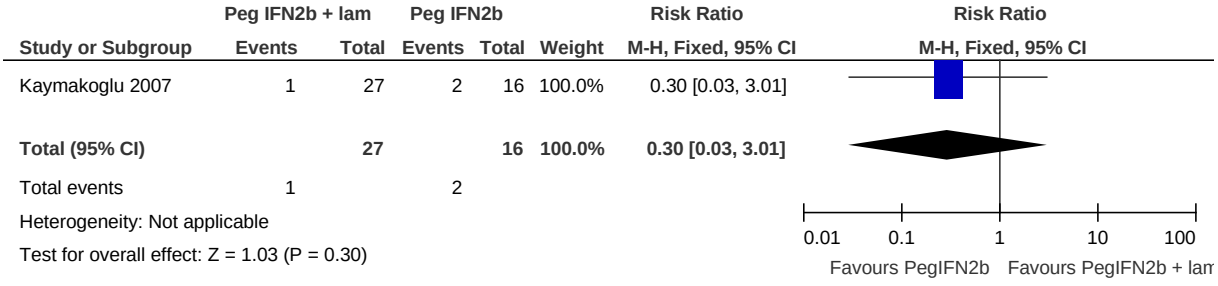


Figure 313: HBsAg seroconversion after 24 weeks follow up.



pegINFa + ADF v PegINFa (HBeAg negative)

Figure 314: Undetectable HBV DNA at end of treatment.

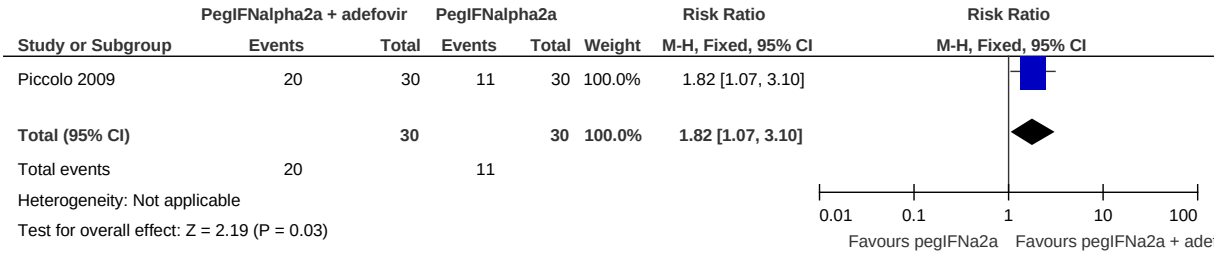


Figure 315: Undetectable HBV DNA at 24 weeks follow up

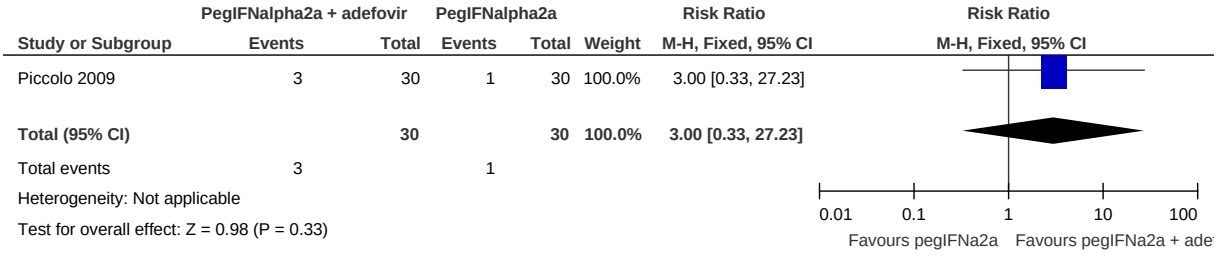


Figure 316: ALT normalisation at end of treatment.

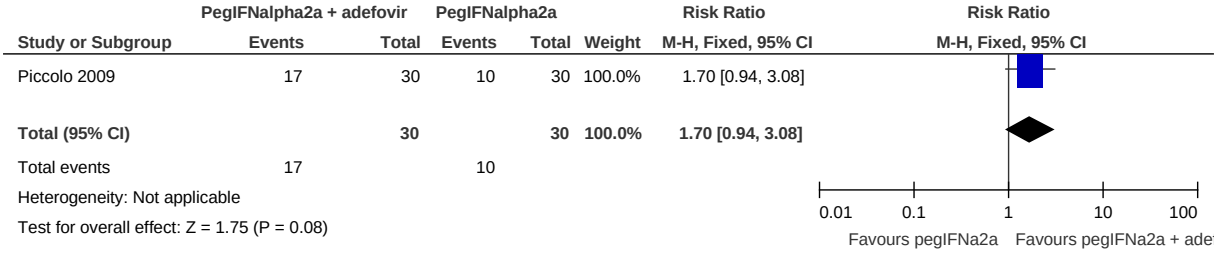


Figure 317: ALT normalisation at 24 weeks follow up.

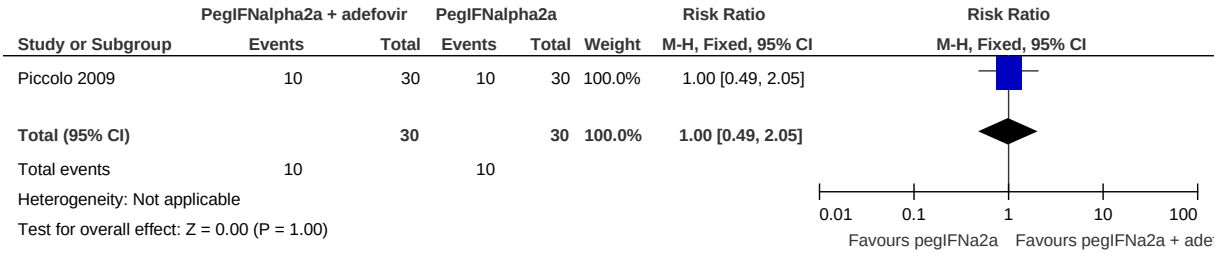
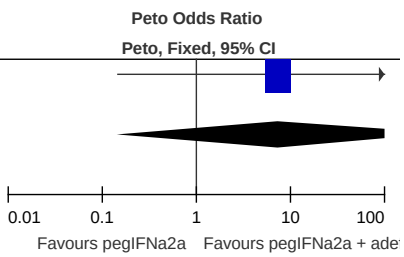


Figure 318: HBsAg loss at 24 weeks follow up.

Study or Subgroup	PegIFNalpha2a + adefovir Events	Total	PegIFNalpha2a Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Piccolo 2009	1	30	0	30	100.0%	7.39 [0.15, 372.38]
Total (95% CI)		**30**		**30**	**100.0%**	**7.39 [0.15, 372.38]**
Total events	1		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.00 (P = 0.32)



INFa + LAM v LAM

Figure 319: Undetectable HBV DNA.

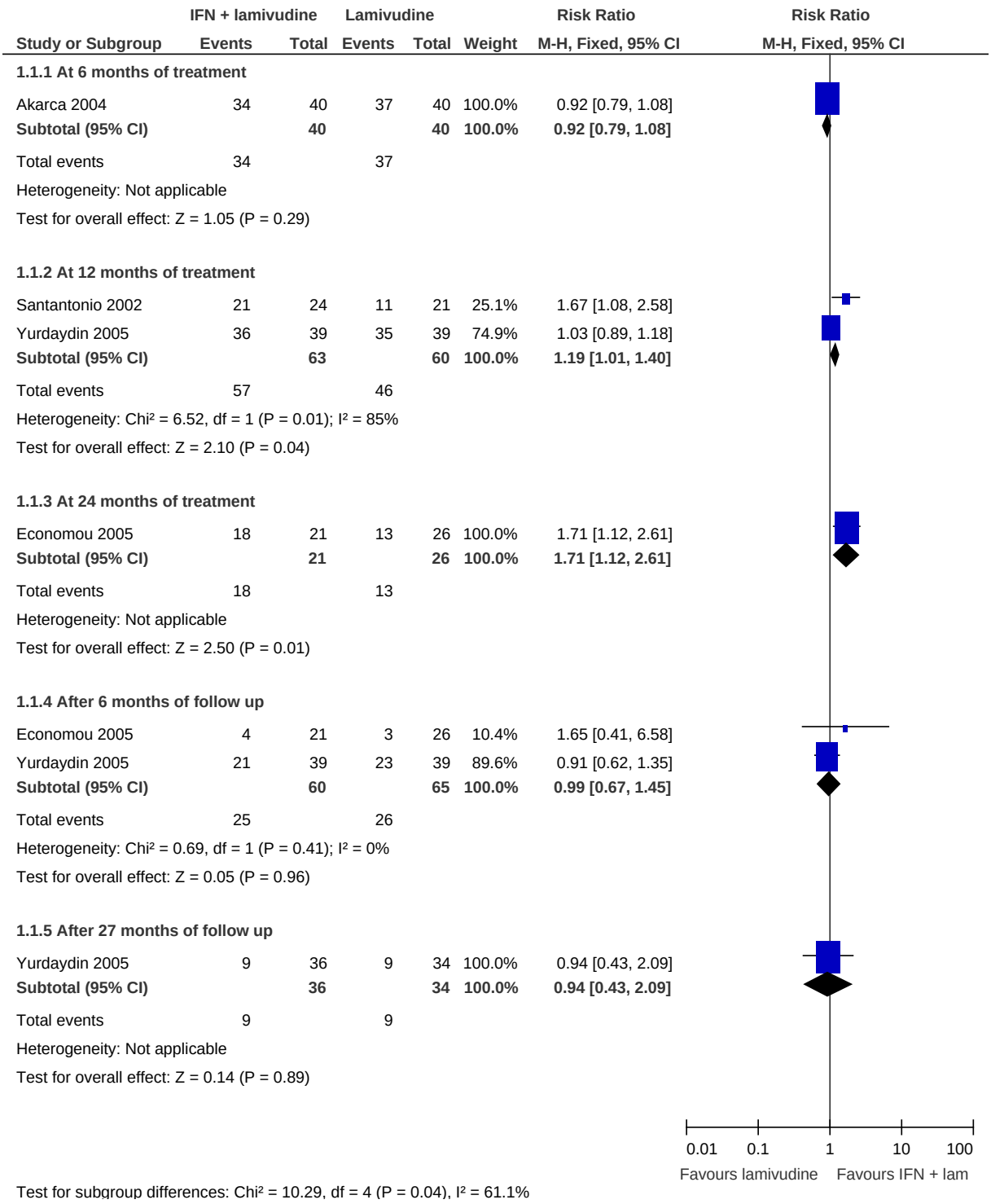


Figure 320: ALT normalisation.

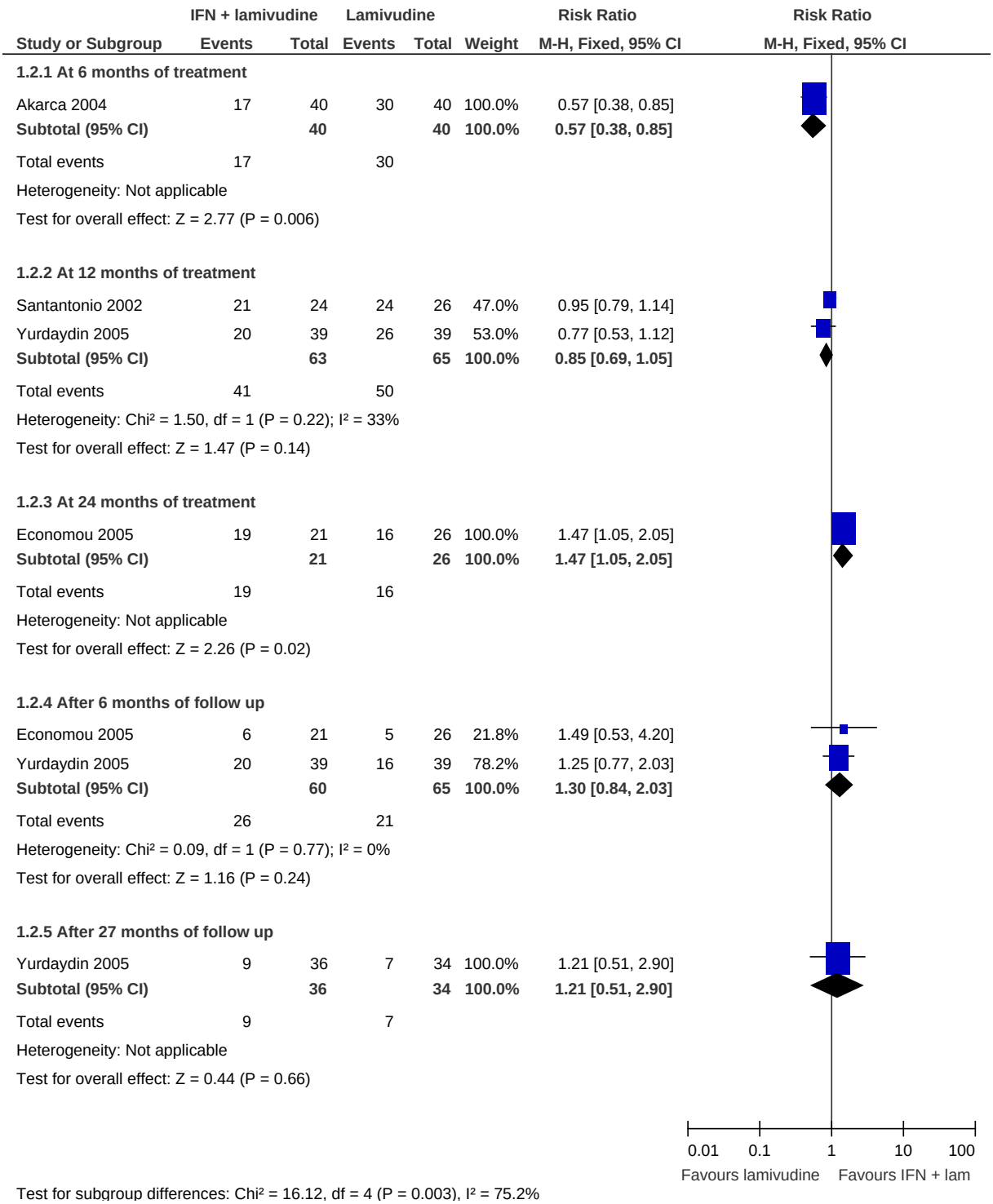


Figure 321: Virological breakthrough.

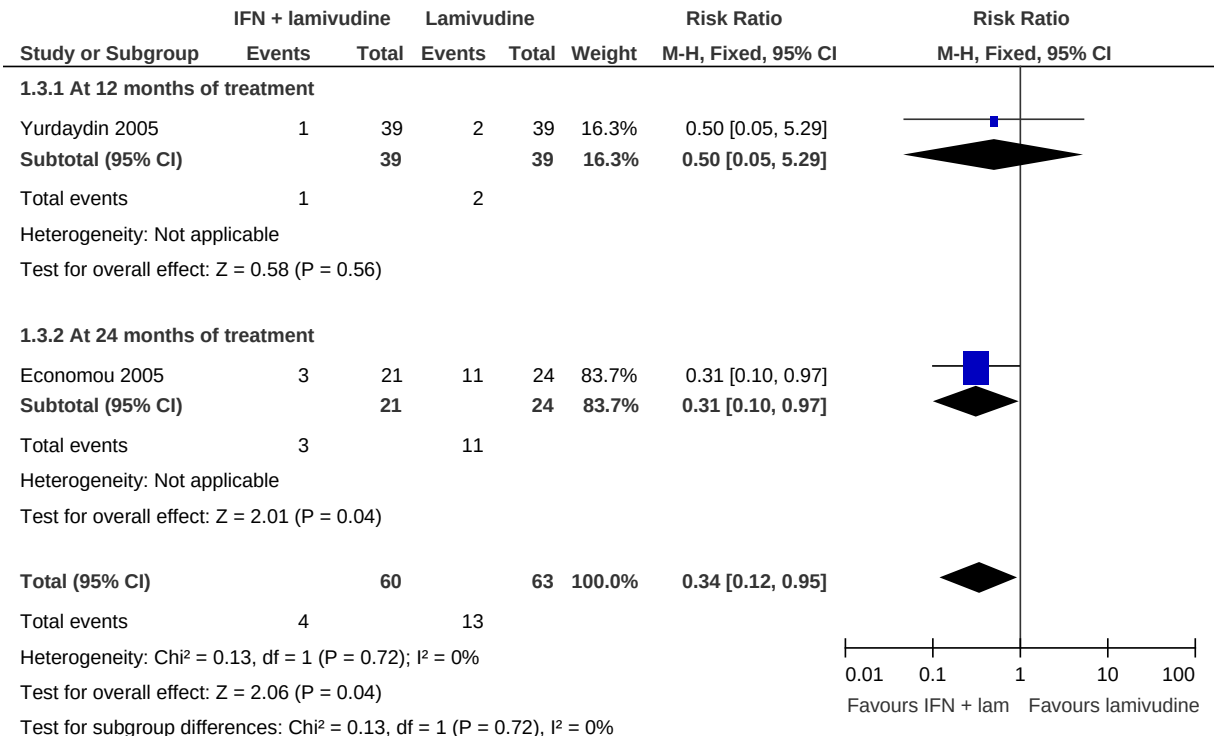


Figure 322: Discontinued due to adverse events.

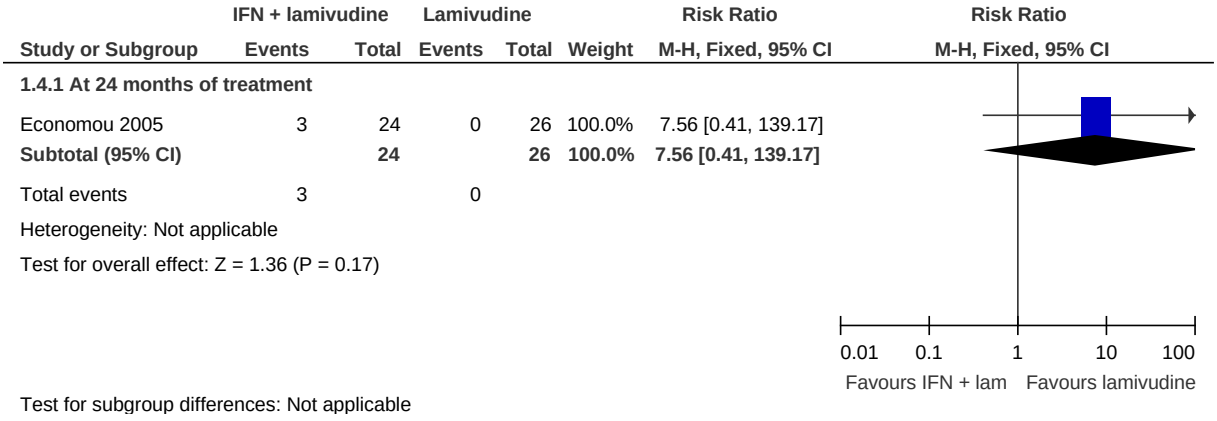


Figure 323: Virological resistance.

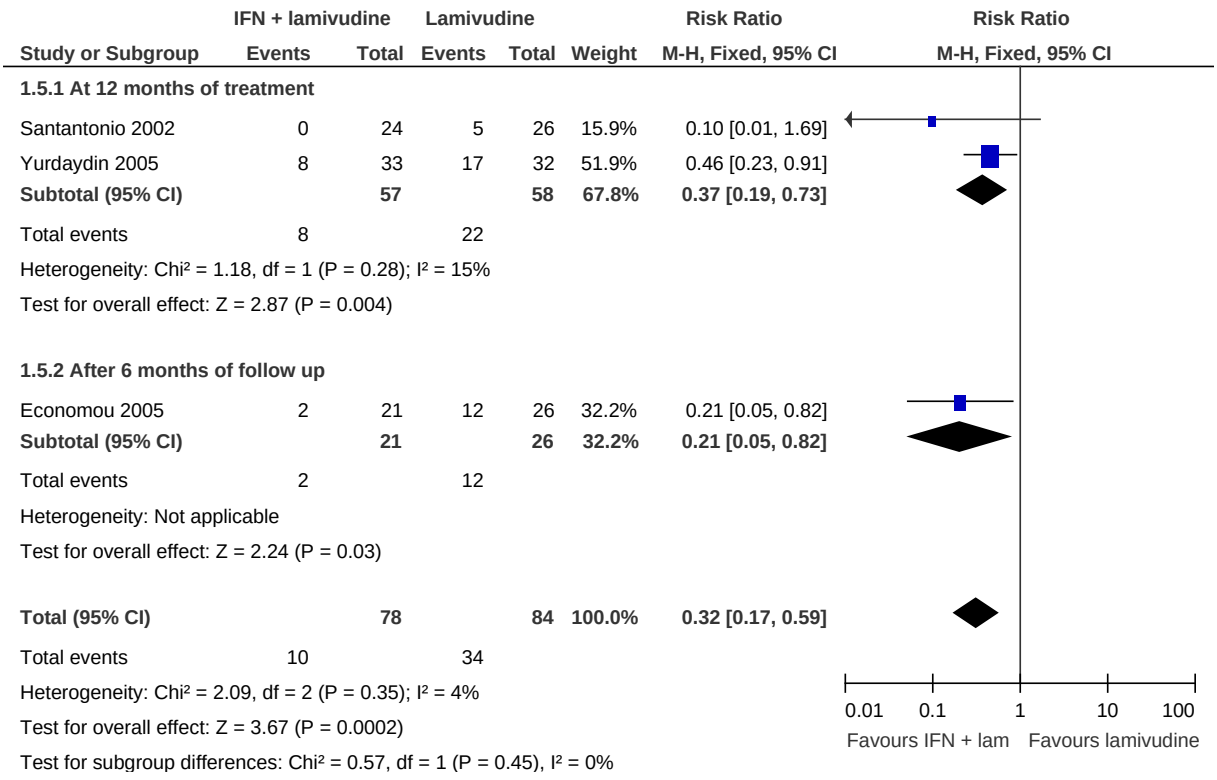
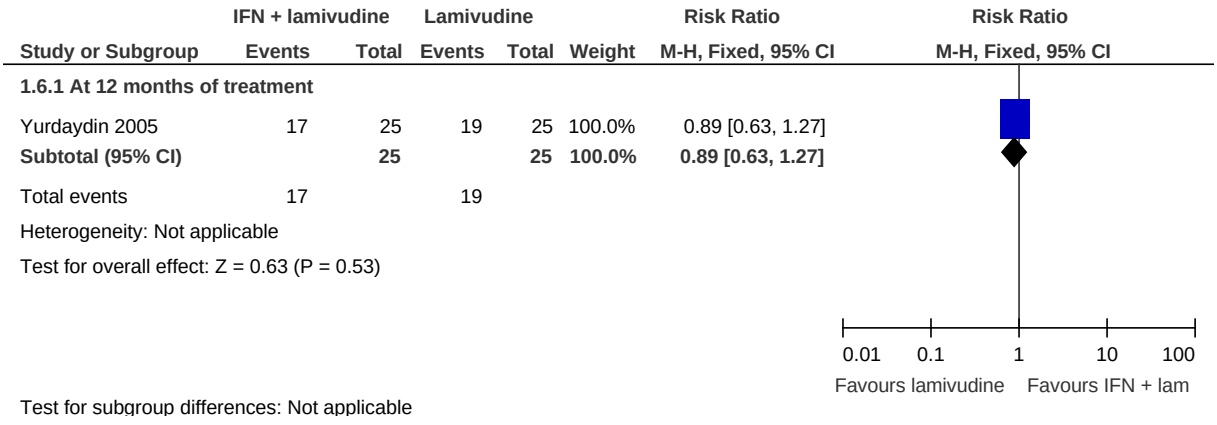


Figure 324: Histological improvement.



Pega2a + LAM v LAM

Figure 325: HBV DNA log reduction (copies/ml) (end of 48 week treatment)

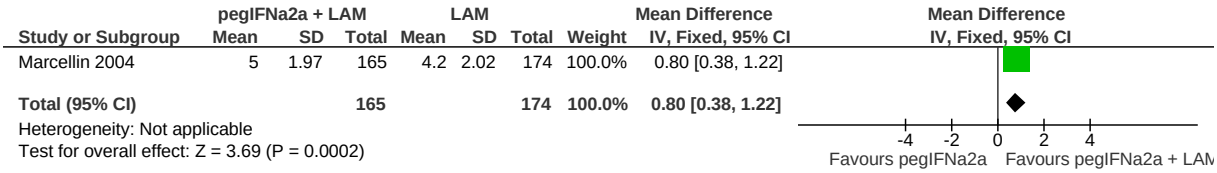


Figure 326: % of patients with detectable HBV DNA (> 20,000 copies/ml(end of 48 week treatment))

Study or Subgroup	pegIFNa2a + LAM Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marcellin 2004	13	162	23	155	100.0%	0.54 [0.28, 1.03]
Total (95% CI)		**162**		**155**	**100.0%**	**0.54 [0.28, 1.03]**
Total events	13		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)

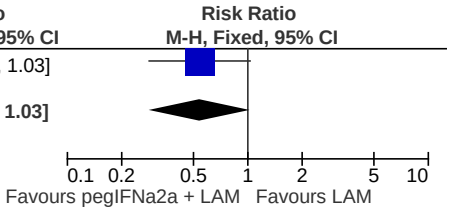


Figure 327: ALT normalization (end of 48 week treatment)

Study or Subgroup	pegIFNa2a + LAM Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marcellin 2004	87	162	132	155	100.0%	0.63 [0.54, 0.74]
Total (95% CI)		**162**		**155**	**100.0%**	**0.63 [0.54, 0.74]**
Total events	87		132			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.74 (P < 0.00001)

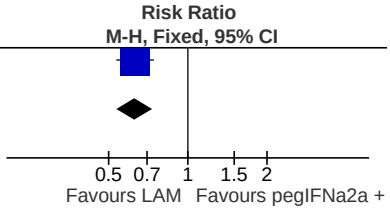


Figure 328: HBV DNA log reduction (copies/ml) (end of 24 week follow up)

Study or Subgroup	pegIFNa2a + LAM Mean	SD	Total	LAM Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Marcellin 2004	2.4	2.99	170	2.3	2.62	165	100.0%	0.10 [-0.50, 0.70]
Total (95% CI)			**170**			**165**	**100.0%**	**0.10 [-0.50, 0.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

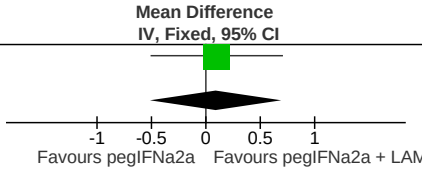


Figure 329: % of patients with detectable HBV DNA (> 20,000 copies/ml(end of 24 week follow up)))

Study or Subgroup	pegIFNa2a + LAM Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marcellin 2004	90	162	110	155	100.0%	0.78 [0.66, 0.93]
Total (95% CI)		**162**		**155**	**100.0%**	**0.78 [0.66, 0.93]**
Total events	90		110			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.81 (P = 0.005)

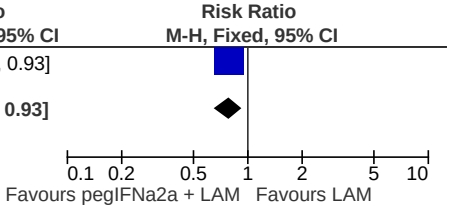


Figure 330: HBsAg loss (end of 24 week follow up)

Study or Subgroup	pegIFNa2a + LAM Events	Total	LAM Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Marcellin 2004	5	162	0	155	100.0%	7.26 [1.24, 42.37]
Total (95% CI)		**162**		**155**	**100.0%**	**7.26 [1.24, 42.37]**
Total events	5		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.20 (P = 0.03)

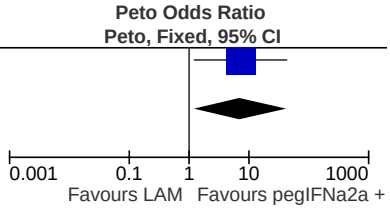


Figure 331: HBsAg seroconversion (end of 24 week follow up)

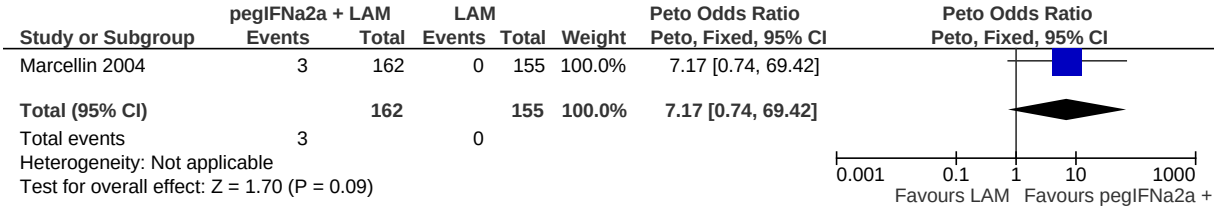


Figure 332: ALT normalization (end of 24 week follow up)

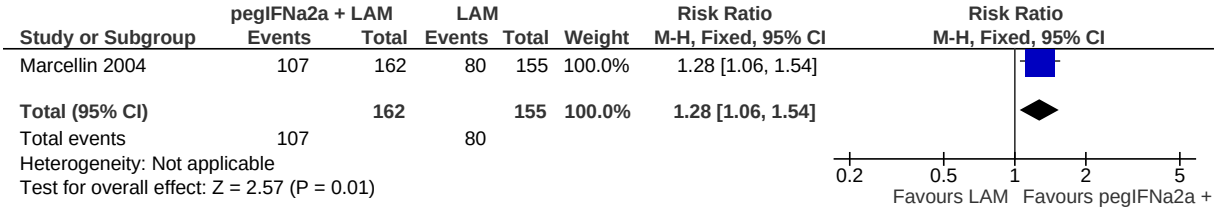


Figure 333: Histologic improvement (end of 24 week follow up)

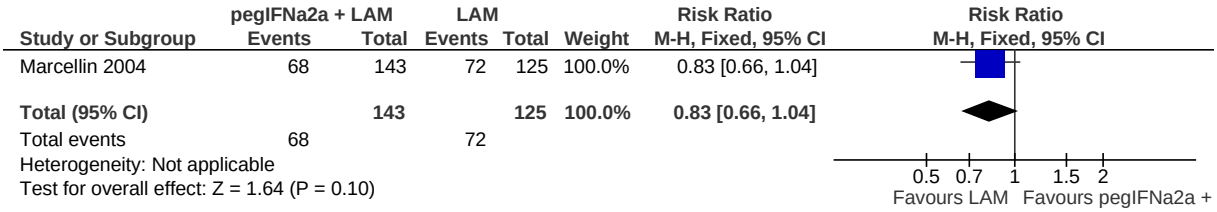
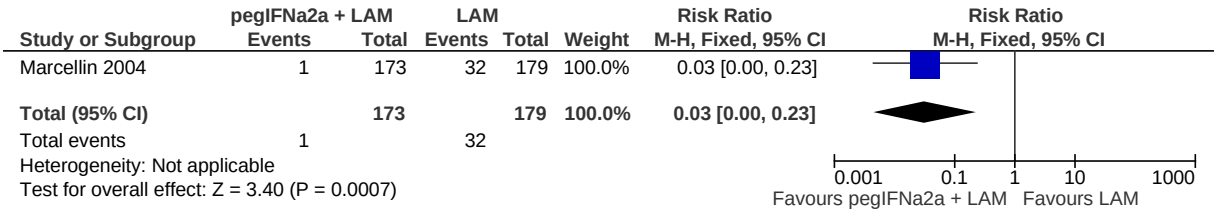


Figure 334: Resistance (genotypic mutation)



ADF + LAM v ADF

G.3.1.4 Pharmacological monotherapies and combination therapies for people co-infected with hepatitis D and C virus

Comparison of interferon alfa-2a versus no treatment

Figure 335: % of people with detectable HDV DNA (assessed at the end of 48 weeks treatment)

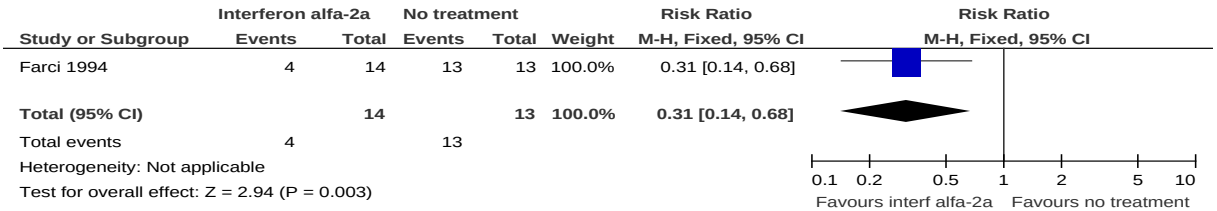


Figure 336: % of people with undetectable HBV DNA (>400 copies/ml)(assessed at the end of 48 weeks treatment)

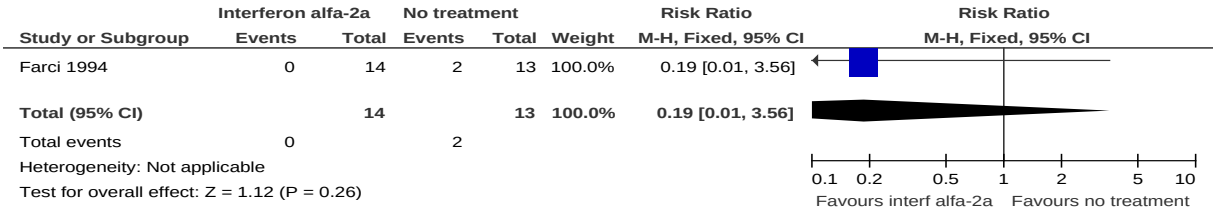


Figure 337: % of people with ALT normalization (assessed at the end of 48 weeks treatment)

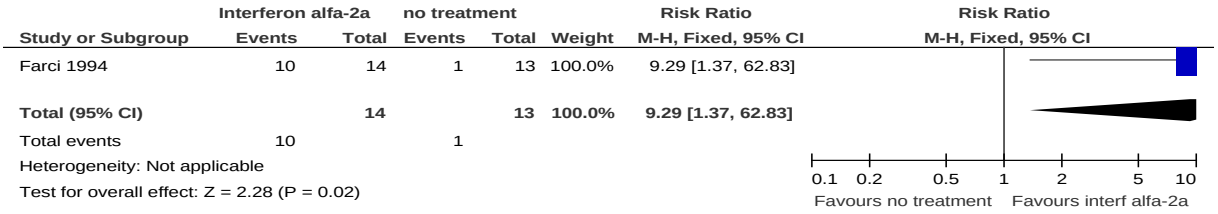


Figure 338: % of people with undetectable HDV DNA (assessed at 6 months follow up)

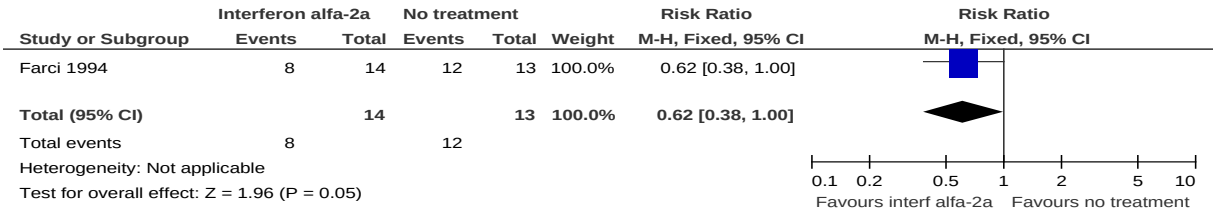


Figure 339: % of people with undetectable HBV DNA (>400 copies/ml) (assessed at 6 months follow up)

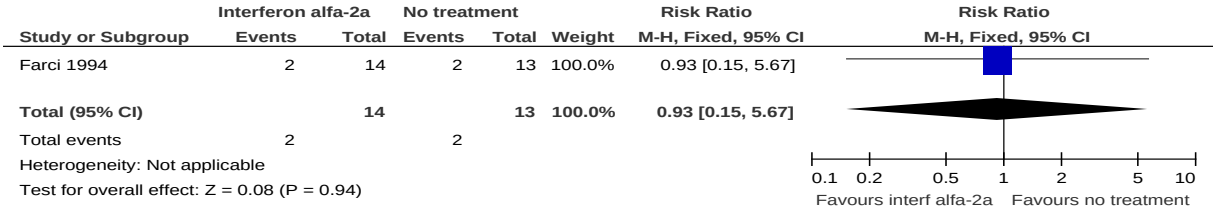


Figure 340: % of people with ALT normalization (assessed at 6 months follow up)

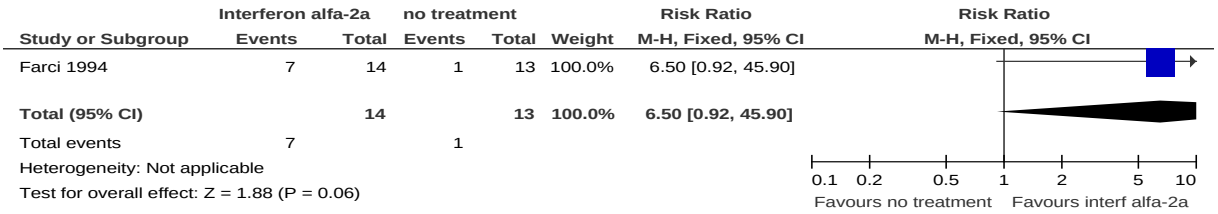


Figure 341: % of people with undetectable HDV DNA (assessed at 12 years follow up)

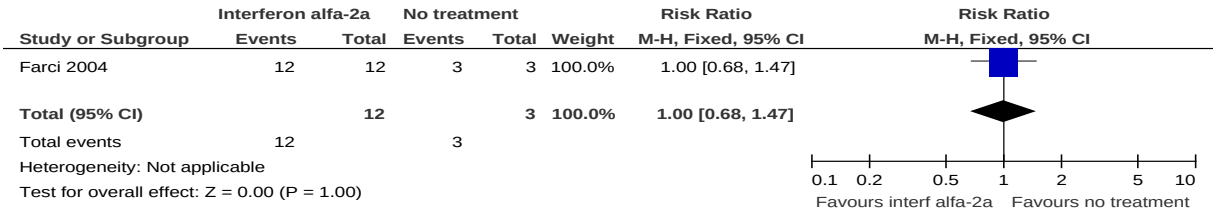


Figure 342: % of people with undetectable HBV DNA (>400 copies/ml) (assessed at 12 years follow up)

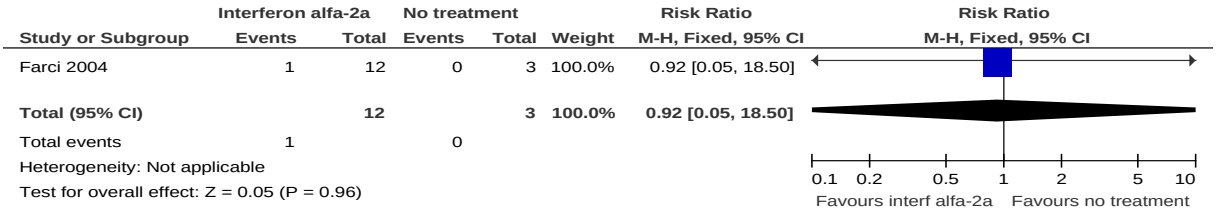


Figure 343: % of people with ALT normalization (assessed at 12 years follow up)

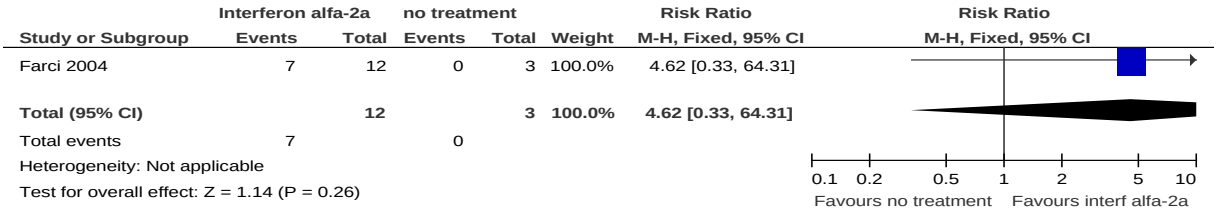


Figure 344: % of people underwent liver transplantation (assessed at 12 years follow up)

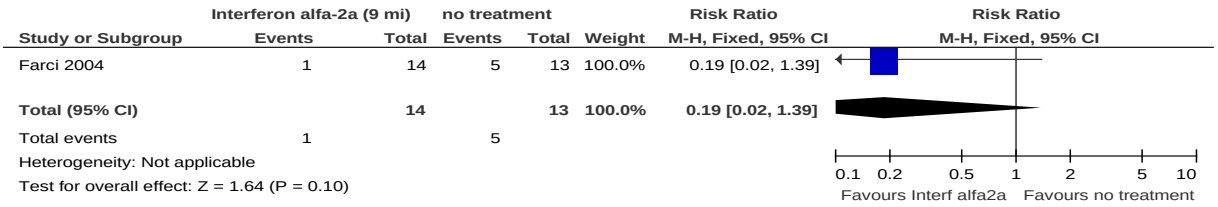
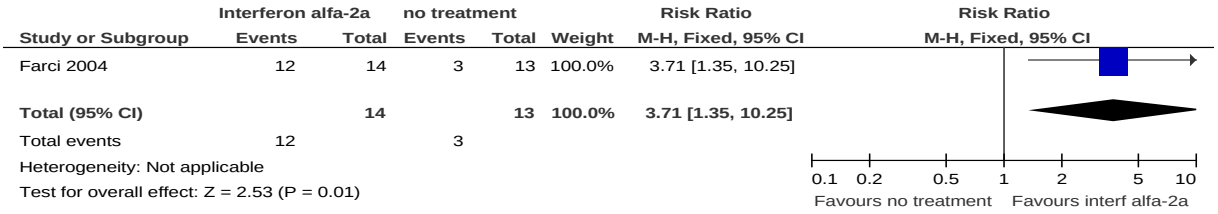


Figure 345: Survival rate



Comparison of Interferon alpha-2b versus no treatment

Figure 346: % of people with ALT normalisation at 1 year

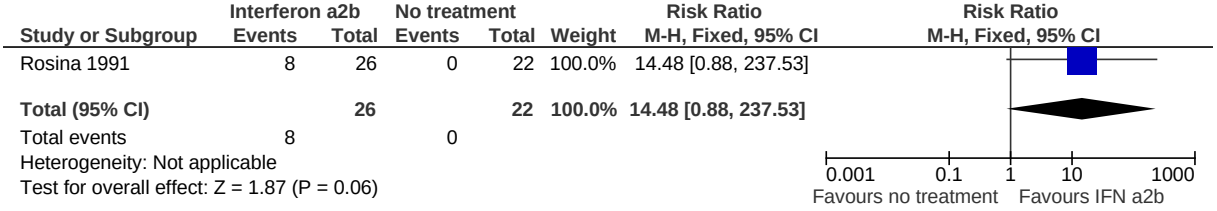
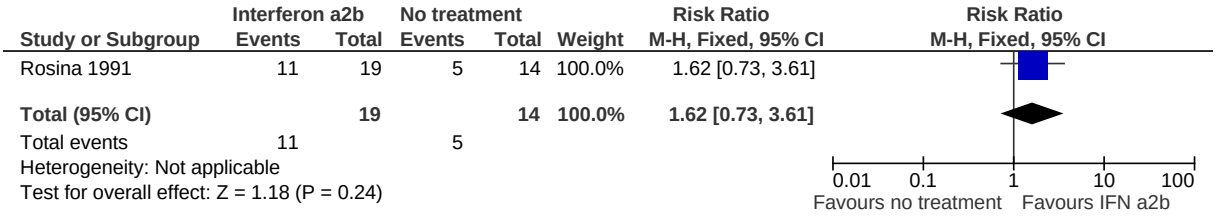


Figure 347: % of people with histologic improvement (definition unclear) at 1 year



Comparison of peginterferon alfa-2a plus adefovir versus adefovir

Figure 348: % of people with undetectable HDV RNA (assessed at the end of 48 week treatment)

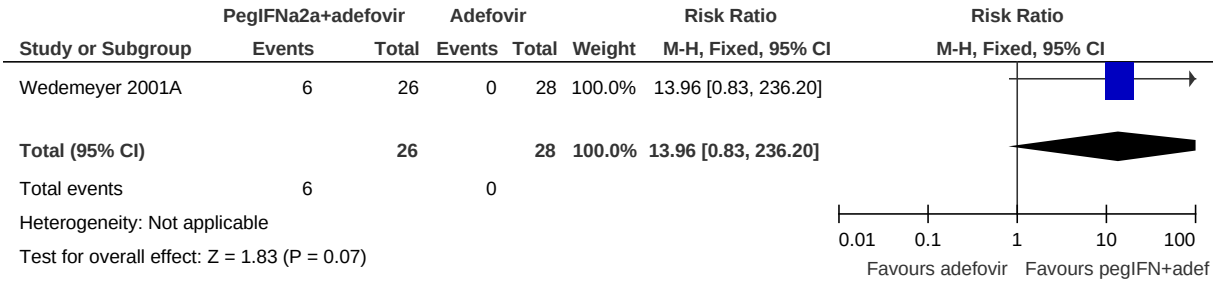


Figure 349: % of people with undetectable HDV RNA (assessed at the end of 24 week follow up)

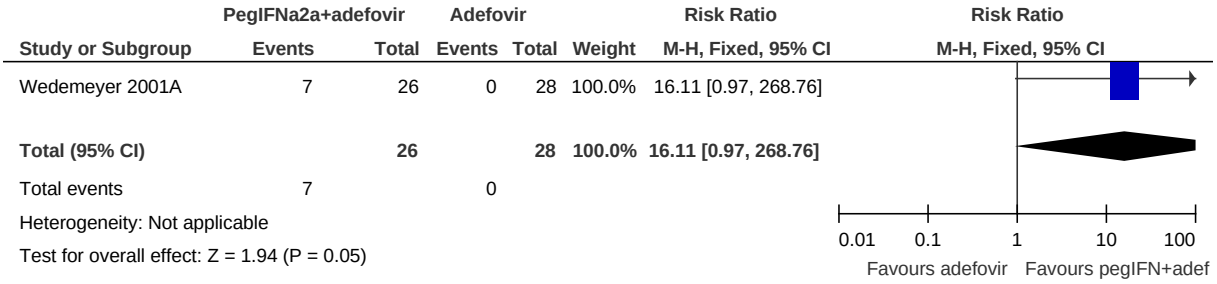


Figure 350: % of people with ALT normalisation (assessed at the end of 48 week treatment)

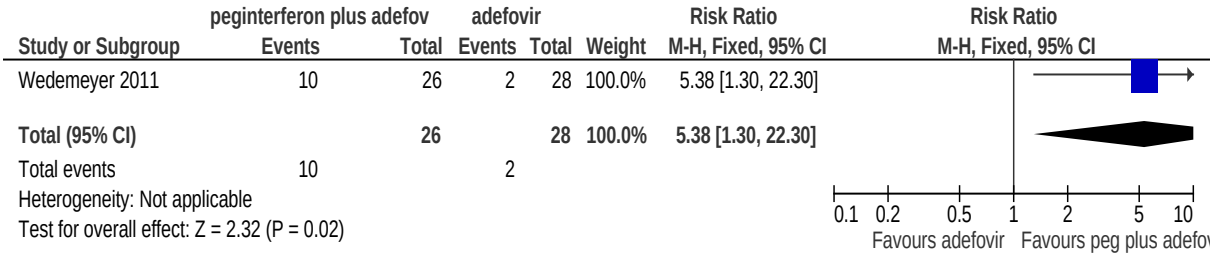
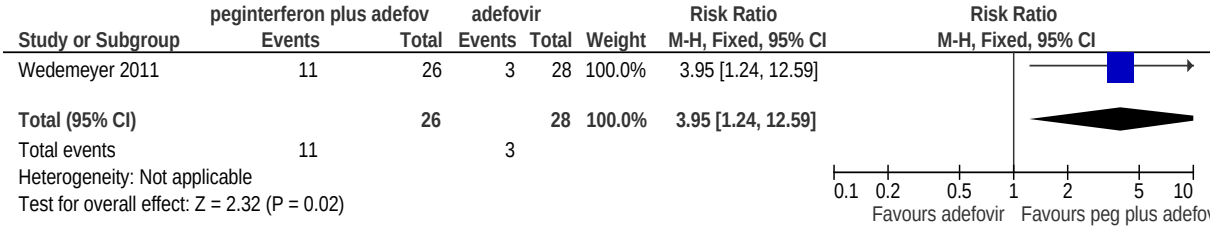


Figure 351: % of people with ALT normalisation (assessed at the end of 24 week follow up)



Comparison of peginterferon alfa-2a plus adefovir versus peginterferon alfa-2a

Figure 352: % of people with undetectable HDV RNA (assessed at the end of 48 week treatment)

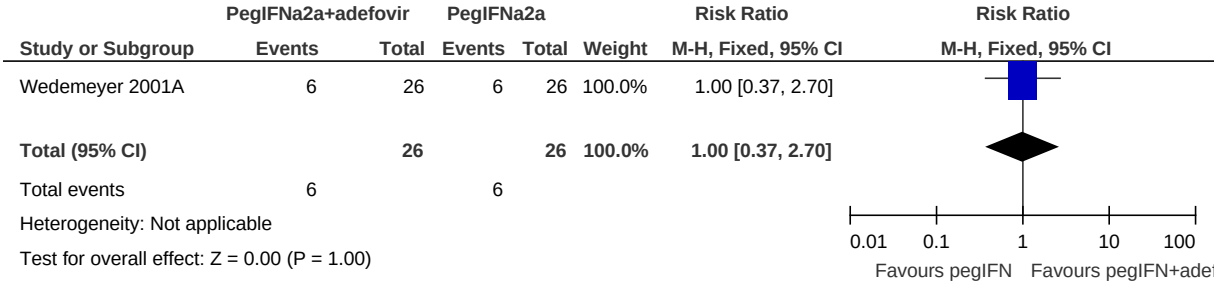


Figure 353: % of people with undetectable HDV RNA (assessed at the end of 24 week follow up)

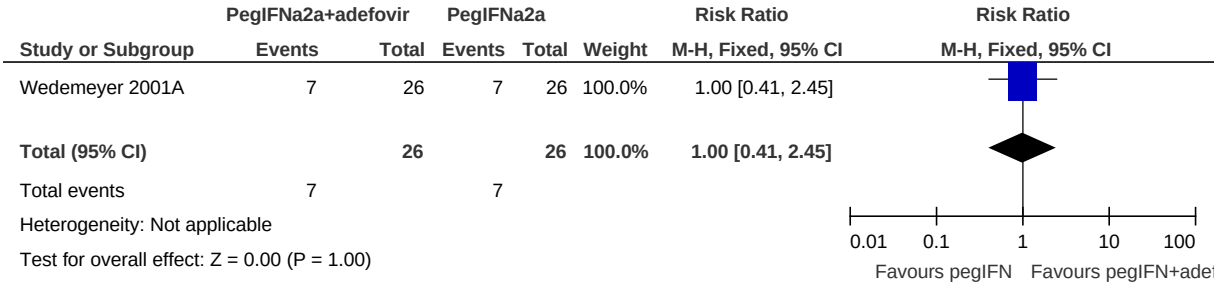


Figure 354: % of people with ALT normalisation (assessed at the end of 48 week treatment)

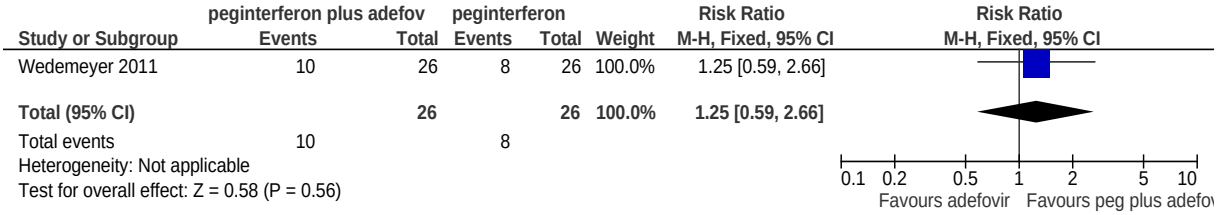
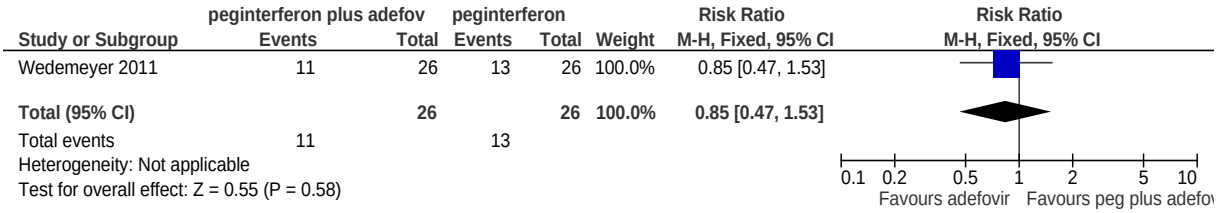


Figure 355: % of people with ALT normalisation (assessed at the end of 24 week follow up)



Comparison of adefovir versus peginterferon alfa-2a

Figure 356: % of people with undetectable HDV RNA (assessed at the end of 48 week treatment)

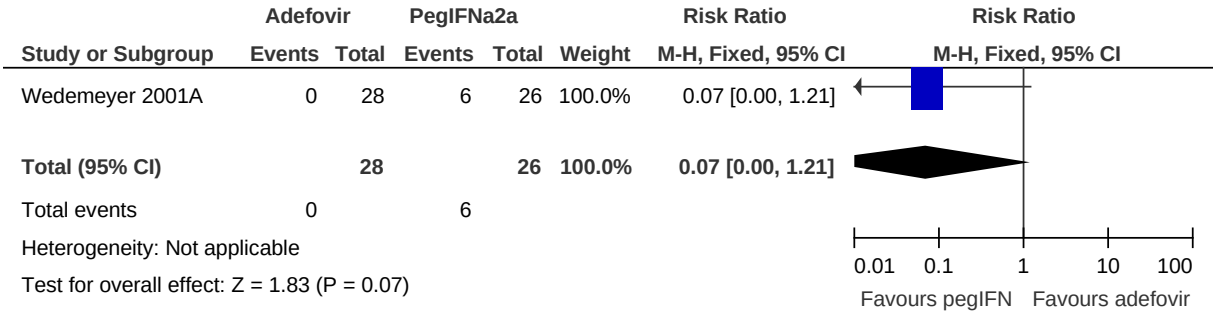


Figure 357: % of people with undetectable HDV RNA (assessed at the end of 24 week follow up)

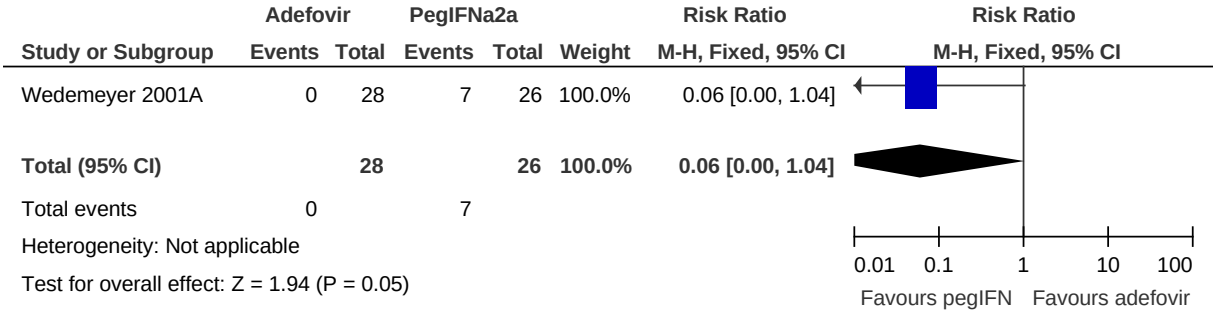


Figure 358: % of people with ALT normalisation (assessed at the end of 48 week treatment)

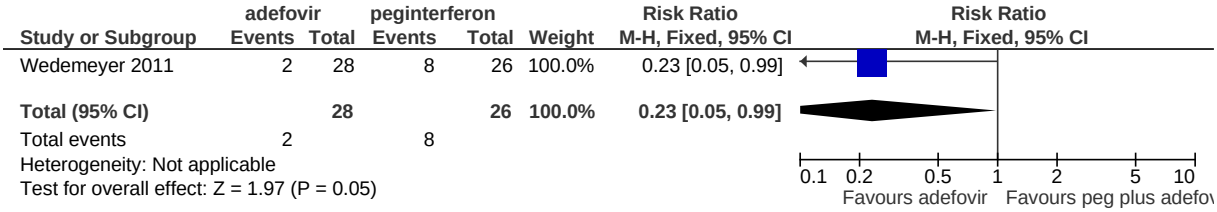
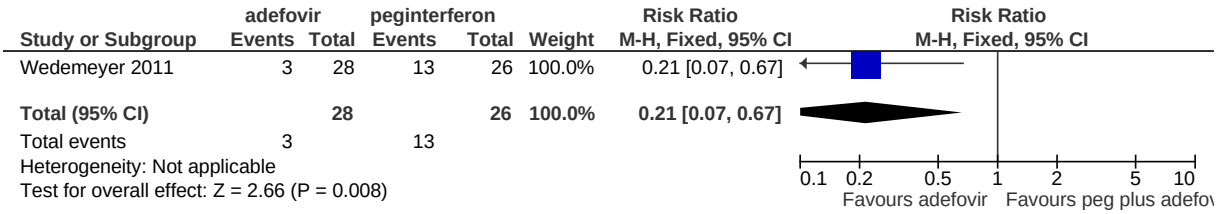


Figure 359: % of people with ALT normalisation (assessed at end of 24 week follow up)



Comparison of interferon alfa-2b plus lamivudine versus interferon alfa-2b

Figure 360: % of people with undetectable HDV DNA (assessed at the end of 48 weeks treatment)

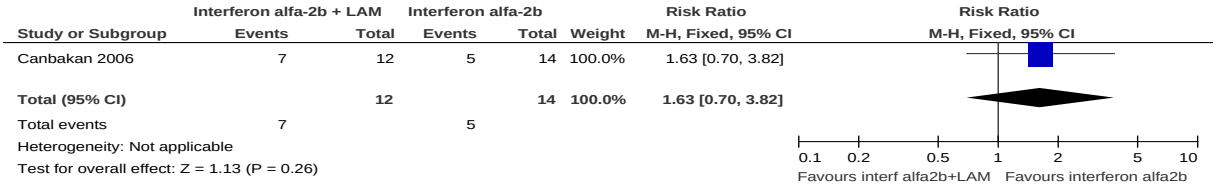


Figure 361: % of people with ALT normalization (assessed at the end of 48 weeks treatment)

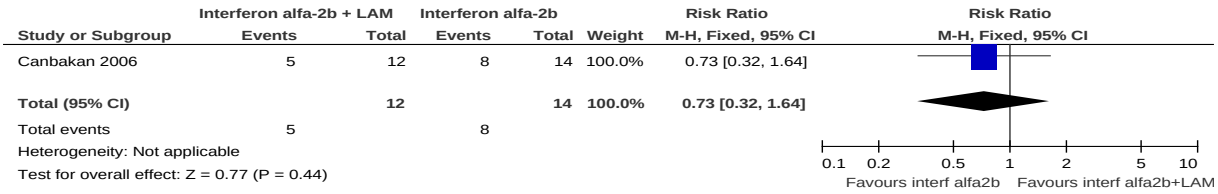


Figure 362: % of people with ALT normalization (assessed at 96 weeks follow up)

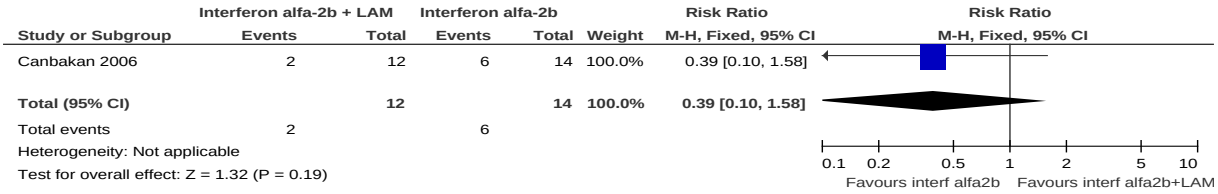


Figure 363: Mortality (assessed at 96 weeks follow up)

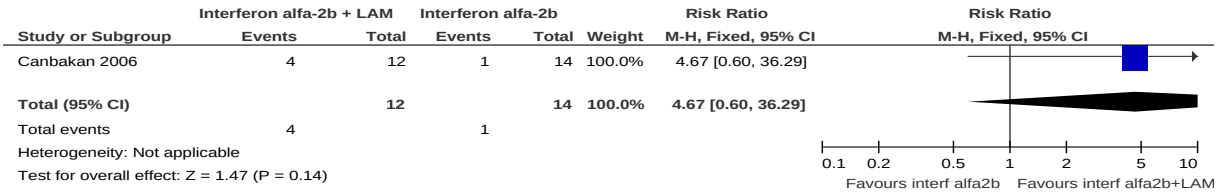
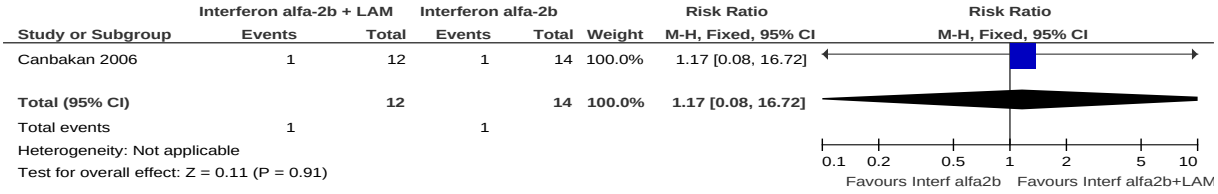


Figure 364: % of people underwent liver transplantation (assessed at 96 weeks follow up)



Comparison of interferon alfa-2a plus lamivudine versus lamivudine

Figure 365: % of people with undetectable HDV DNA (assessed at the end of 12 months treatment)

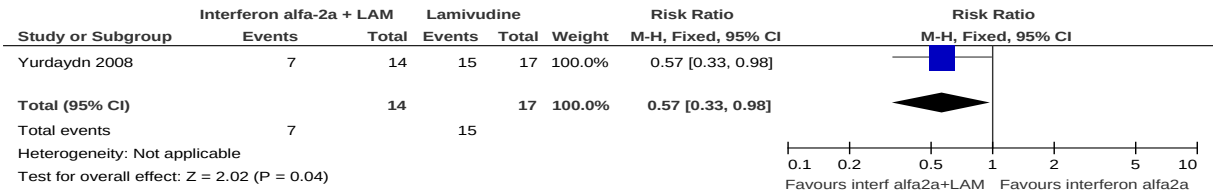


Figure 366: % of people with ALT normalization (assessed at the end of 12 months treatment)

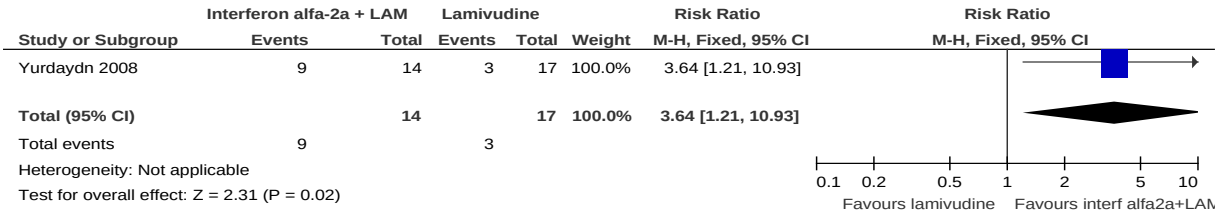


Figure 367: % of people with undetectable HDV DNA (assessed at 6 months follow up)

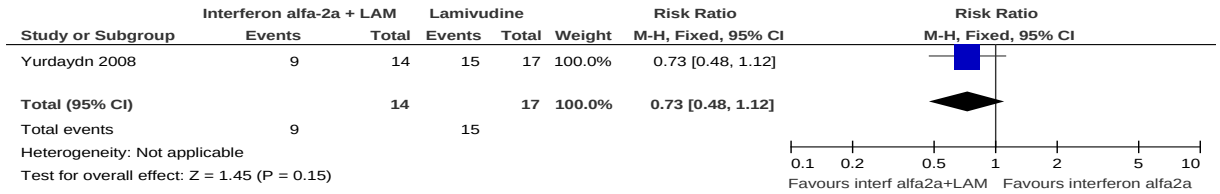
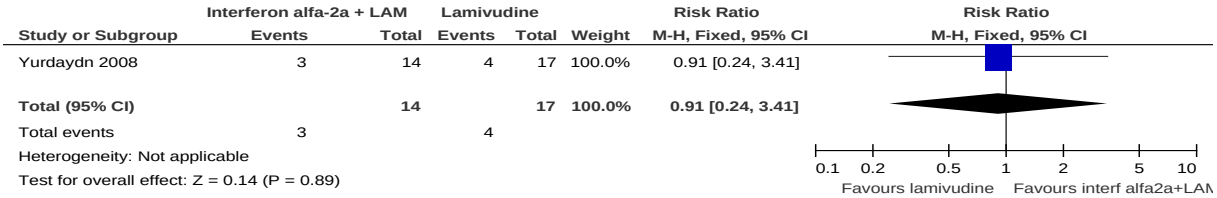
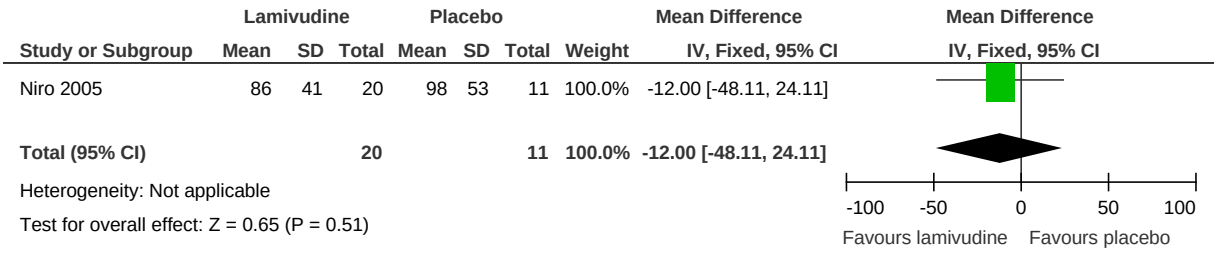


Figure 368: % of people with ALT normalization (assessed at 6 months follow up)



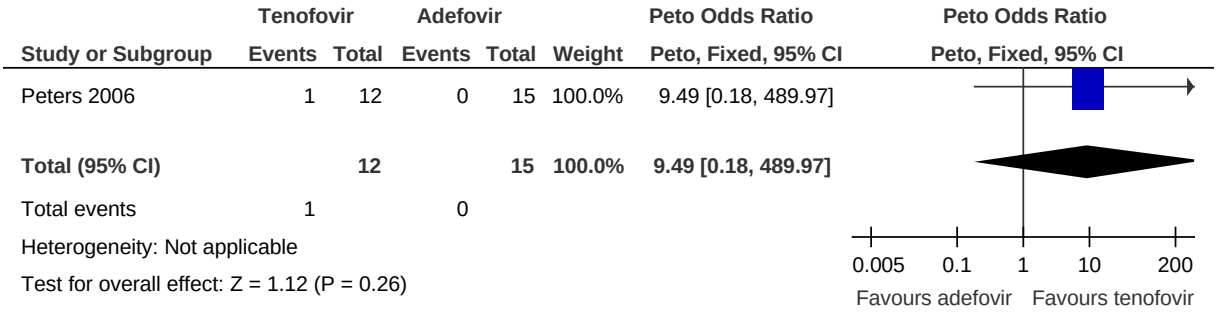
Lamivudine versus placebo in patients coinfected with HDV

Figure 369: **ALT U/L at end of 52 weeks treatment.**



Tenofovir versus adefovir in patients coninfected with HBV and HIV

Figure 370: HBeAg seroconversion at week 48 of treatment



New Forest plots for new study Chan 2012: patients with decompensated cirrhosis: Telbivudine versus lamivudine (treatment naive; mixed HBeAg positive and negative)

Figure 371: HBV DNA <10,000 copies/mL.

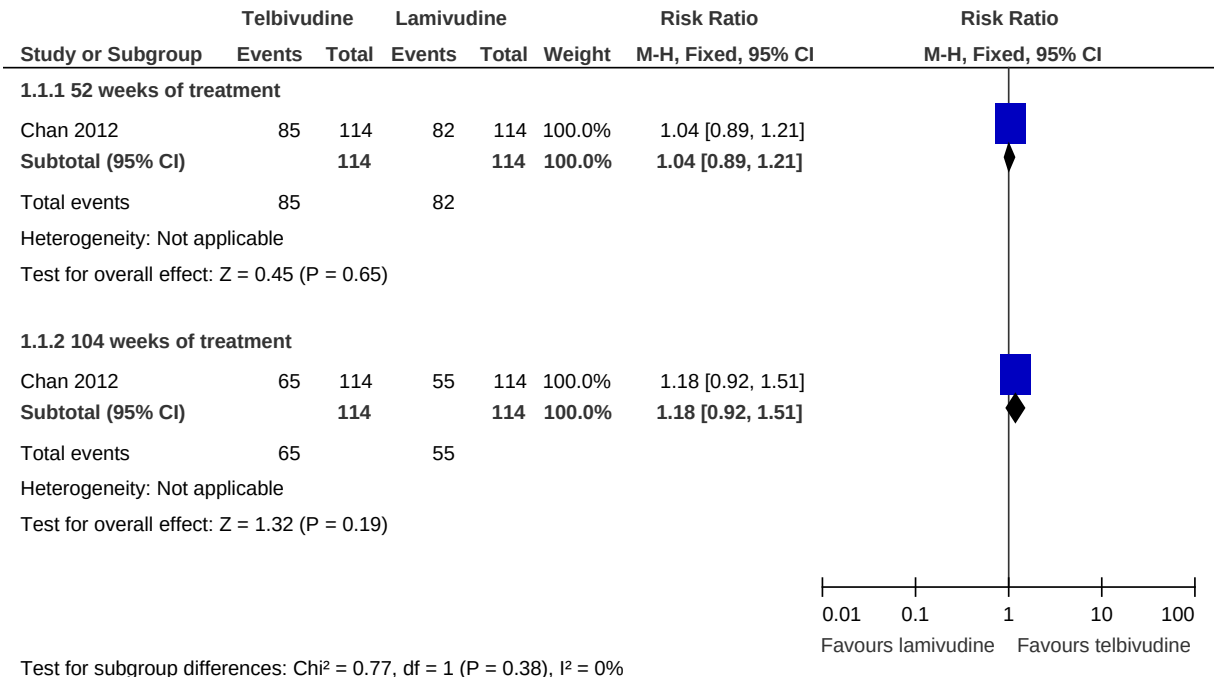


Figure 372: Undetectable HBV DNA <300 copies/mL.

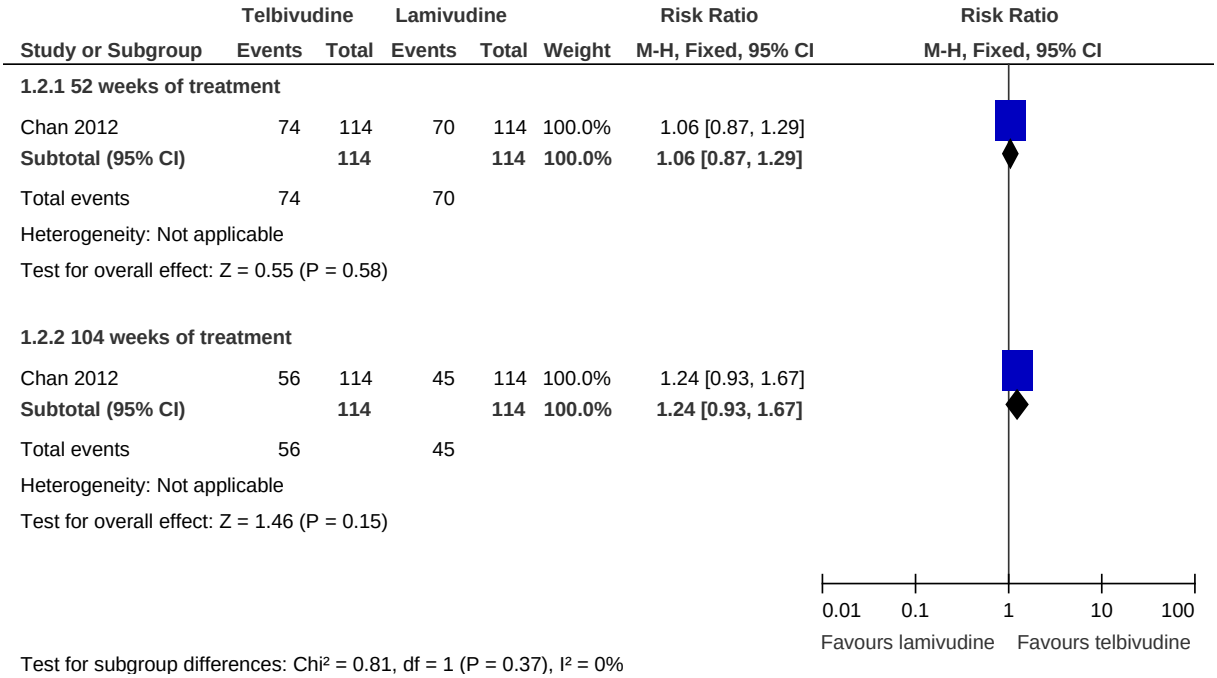


Figure 373: ALT normalisation.

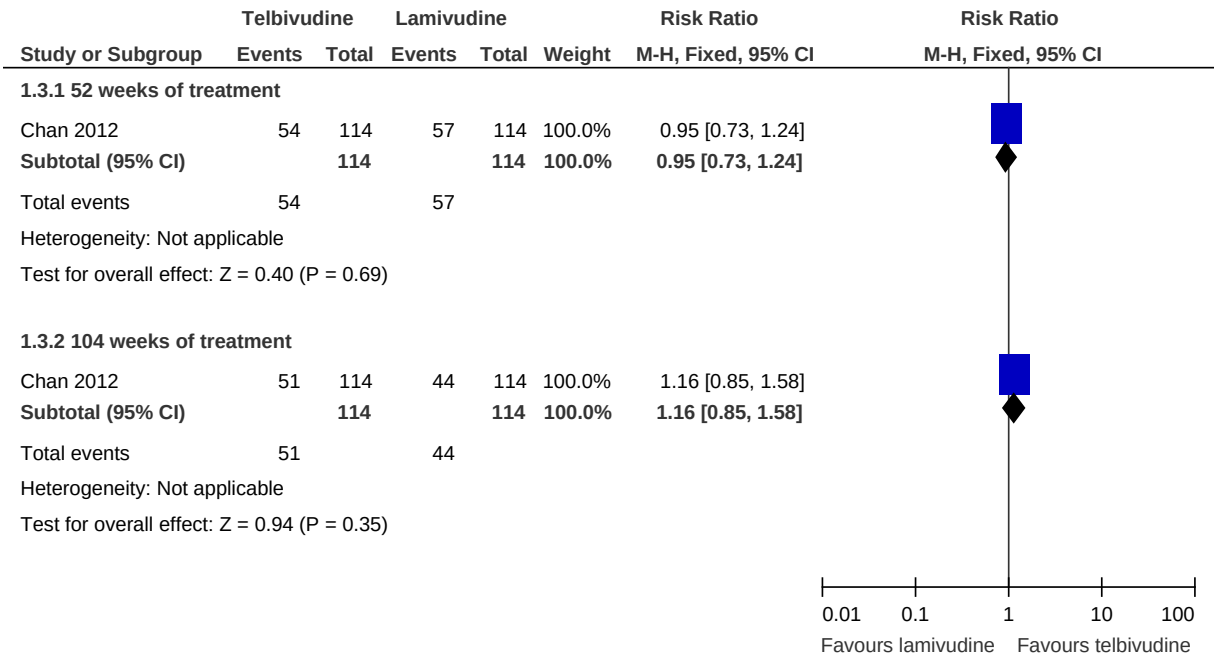
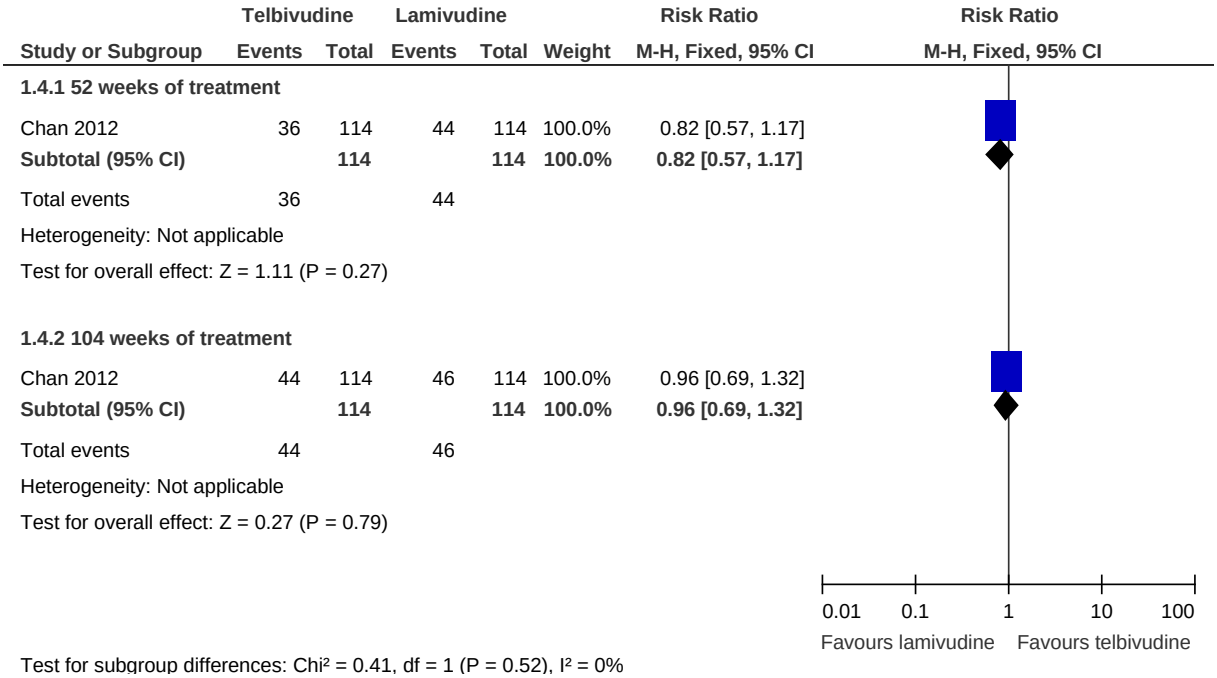


Figure 374: Histological improvement.



G.3.1.5 Pharmacological monotherapies and combination therapies in achieving remission of the action of CHB infection for children

ADF vs. PLACEBO

Figure 375: ALT normalisation [end of treatment- week 48]

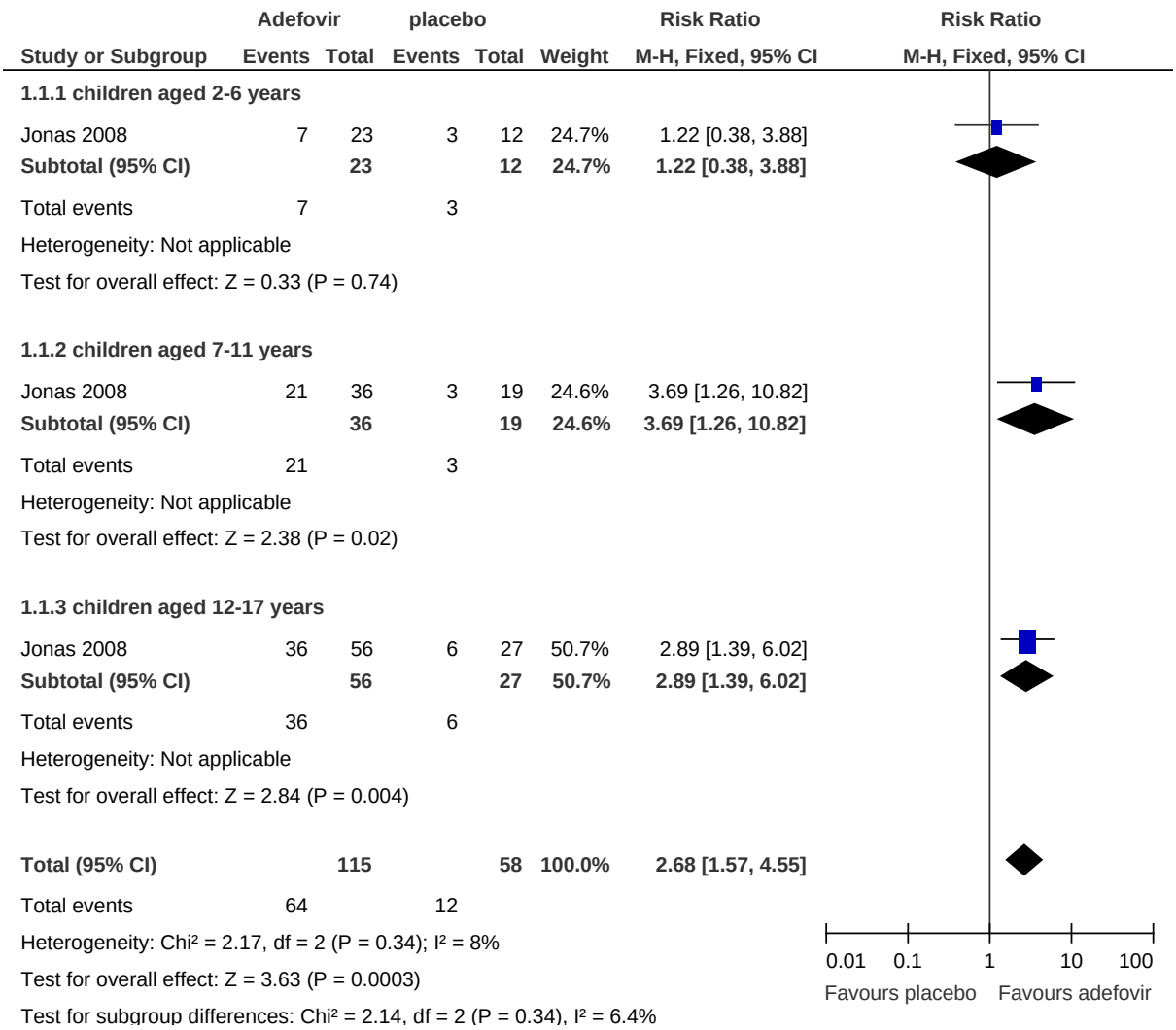


Figure 376: Undetectable HBV DNA (<169 copies/mL) [end of treatment- week 48]

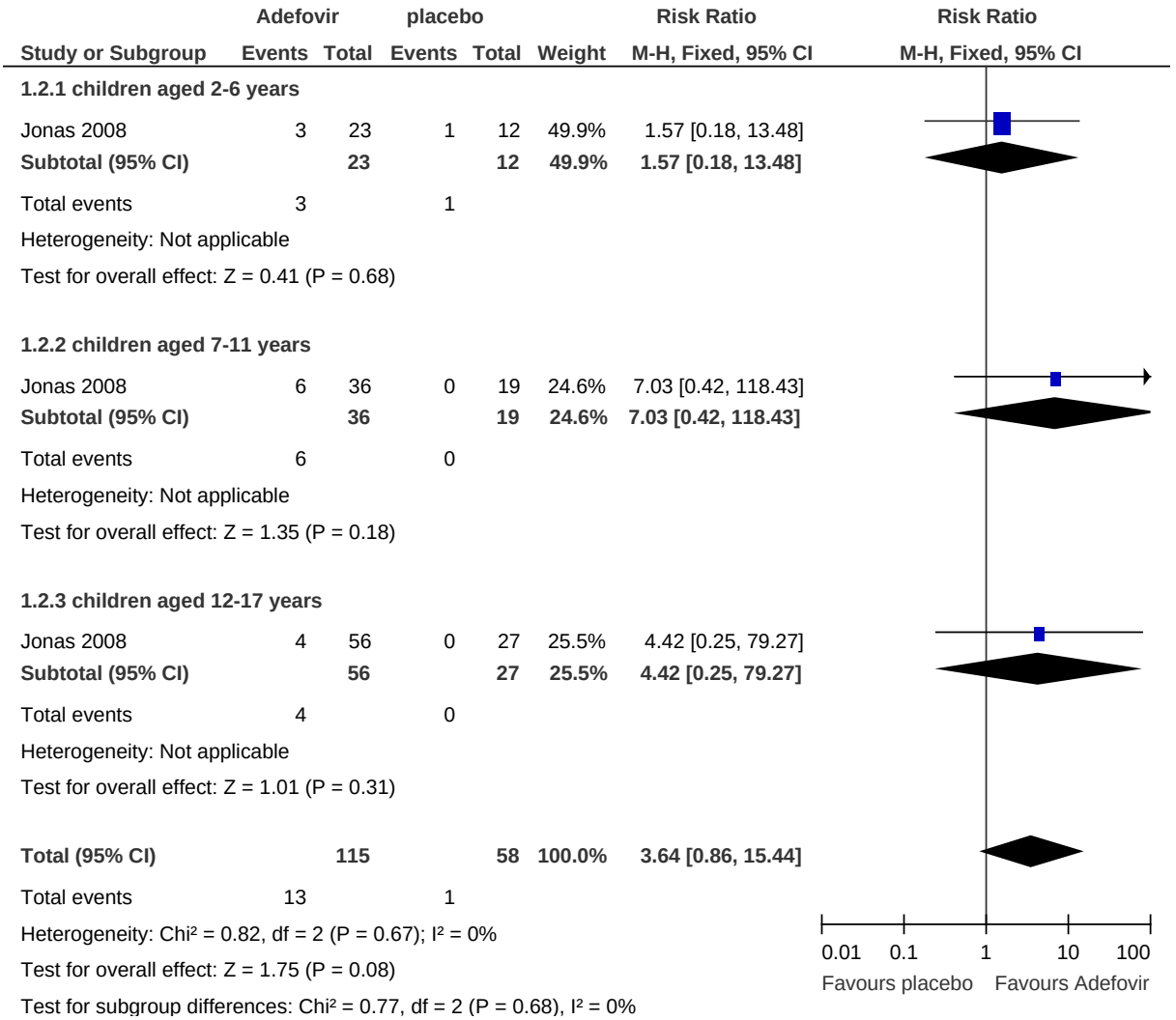


Figure 377: HBsAg seroconversion [end of treatment- week 48]

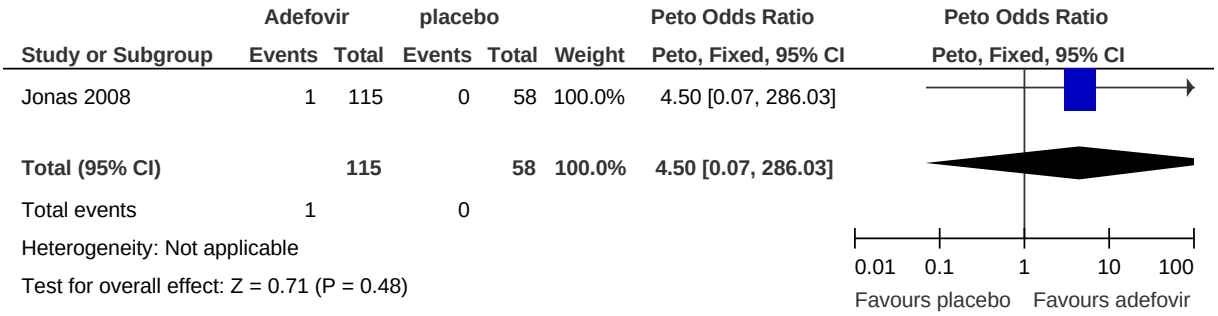


Figure 378: Incidence of resistance

Figure 379: HBeAg seroconversion [end of treatment- week 48]

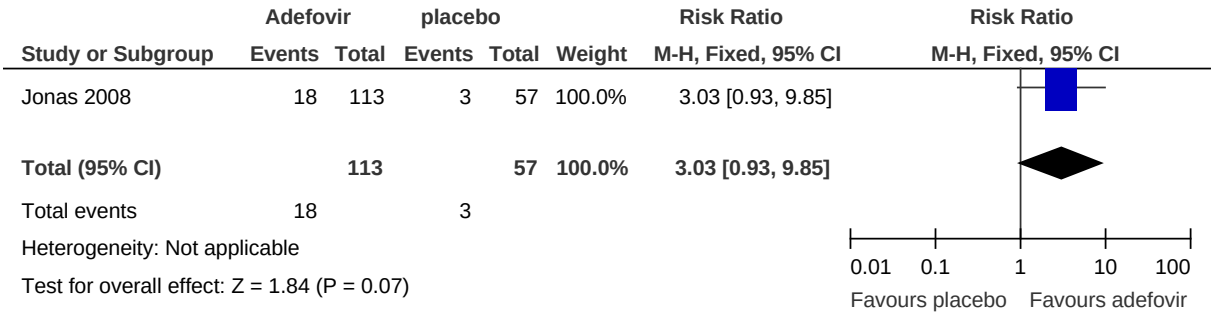


Figure 380: Withdrawal due to adverse events [end of treatment- week 48]

INF-α 2a + LAM vs. INF-α 2b + LAM

Figure 381: ALT normalisation [end of treatment - 12 months]

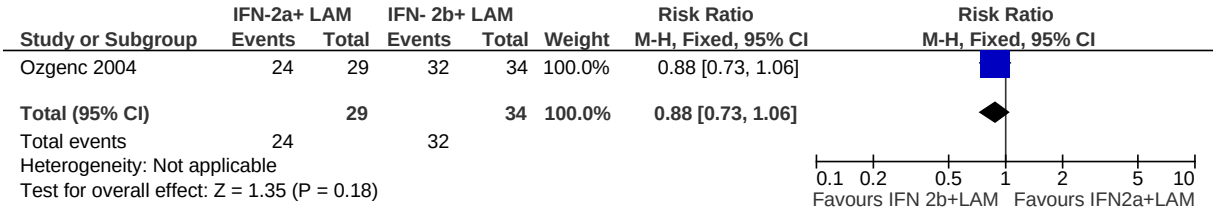


Figure 382: Anti-HBe seroconversion [end of treatment - 12 monthss

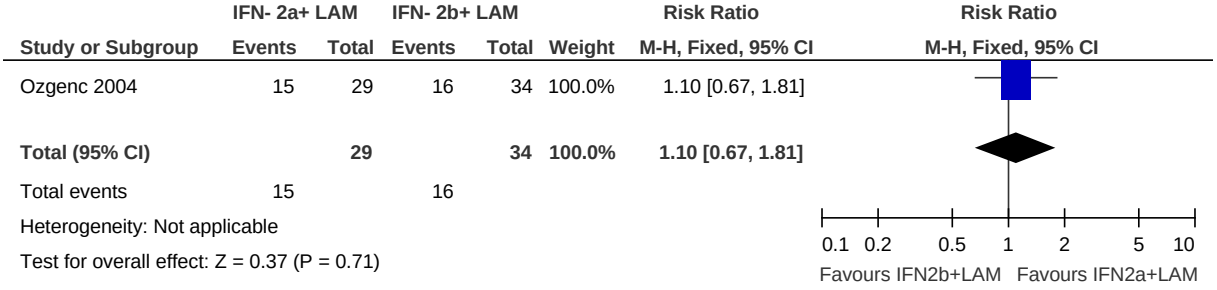


Figure 383: Anti-HBs seroconversion [end of treatment - 12 months]

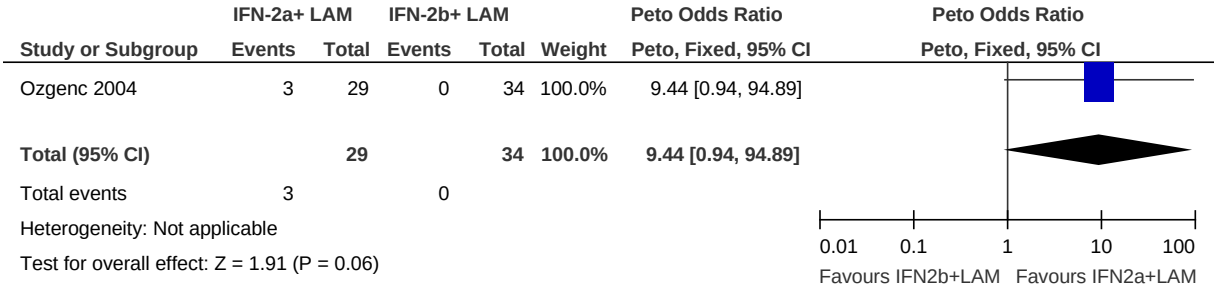


Figure 384: Undetectable DNA (<5pg/mL) [end of treatment - 12 months]

Figure 385: Response (DNA clearance, HBeAg seroconversion and ALT normalization) (6 months follow up after treatment).

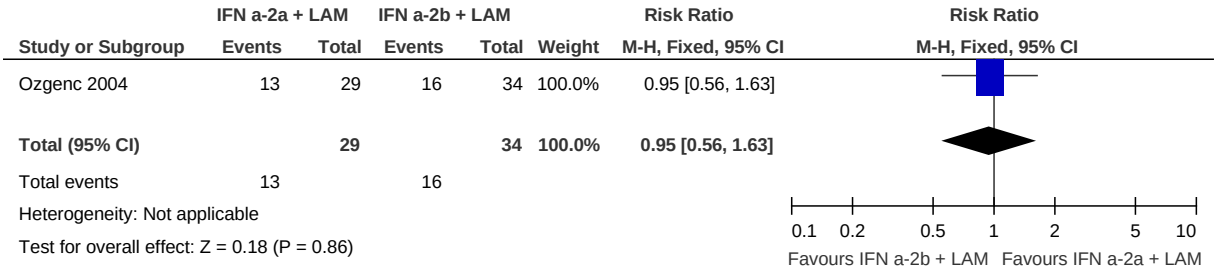
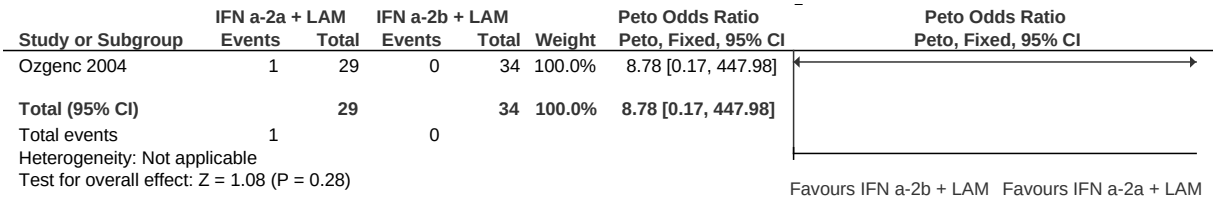
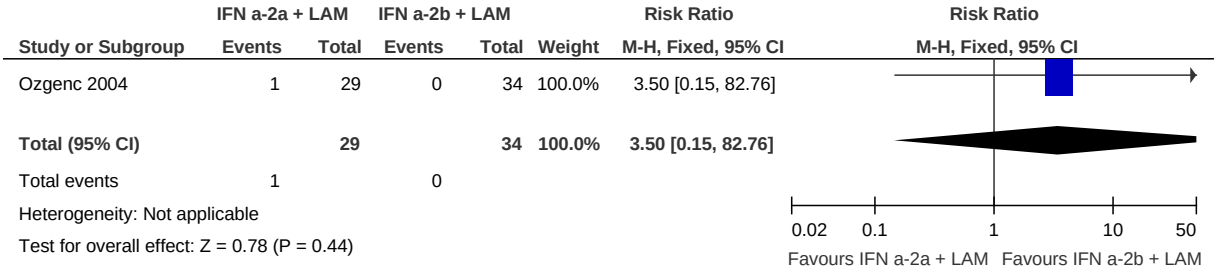


Figure 386: Breakthrough (re-emergence of HBV DNA after clearance, mutations not studied (end of treatment - 12 months).





INF-α 2b vs. no treatment

Figure 387: ALT normalisation [week 48 – 24 weeks after end of treatment]

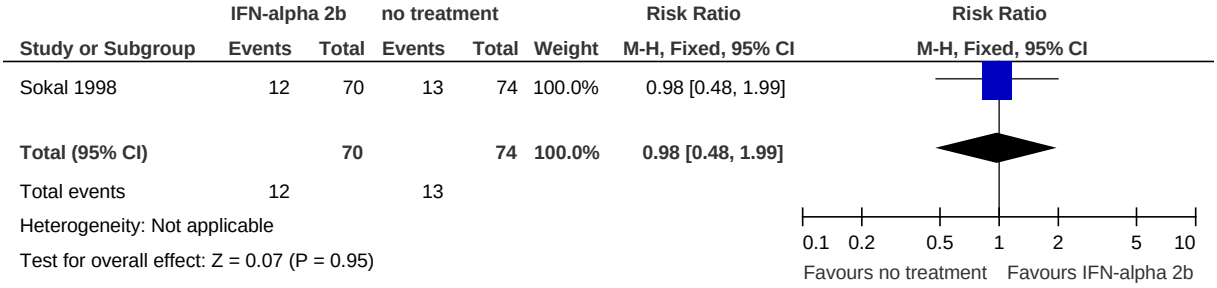


Figure 388: HBsAg loss [week 48 – 24 weeks after end of treatment]

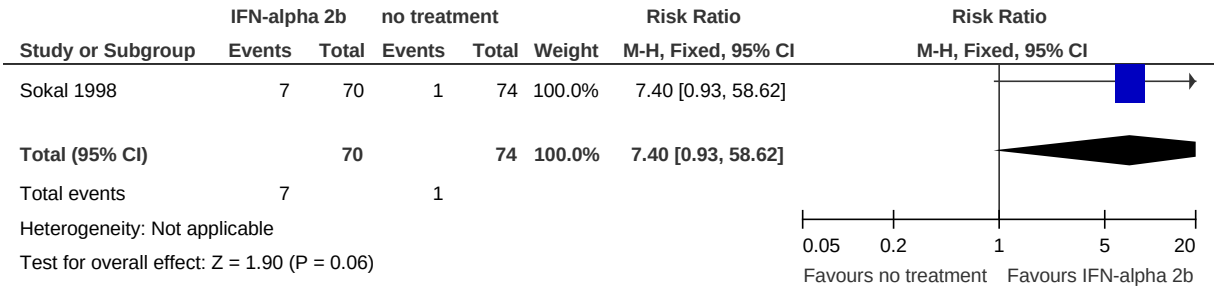


Figure 389: Undetectable HBV DNA (<1.6pg/mL) [end of treatment- week 24].

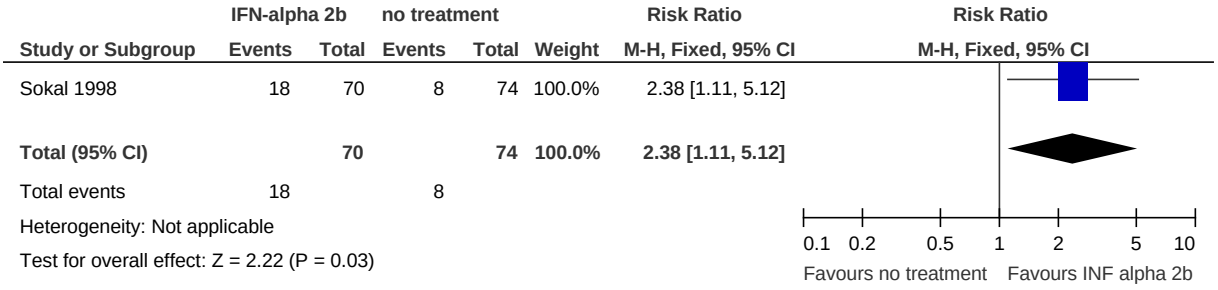


Figure 390: Undetectable HBV DNA (<1.6pg/mL) at week 48 (24 weeks after end of treatment).

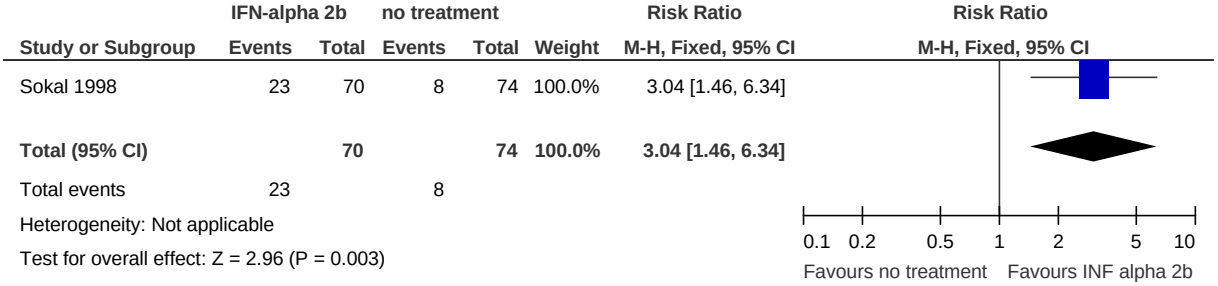


Figure 391: HBeAg loss at week 48 (24 weeks after end of treatment).

LAM vs. PLACEBO

Figure 392: ALT normalisation [end of treatment- week 52]

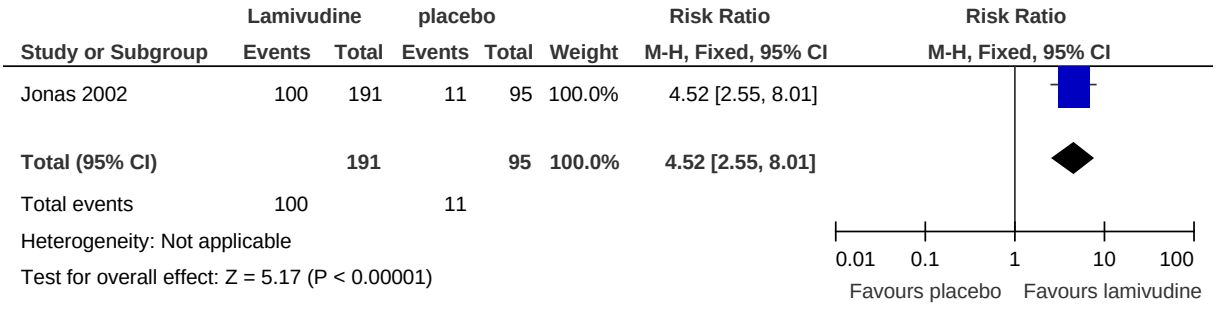


Figure 393: Loss of HBeAg [end of treatment- week 52)]

Study or Subgroup	Lamivudine Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jonas 2002	50	191	14	95	100.0%	1.78 [1.04, 3.05]
Total (95% CI)		**191**		**95**	**100.0%**	**1.78 [1.04, 3.05]**
Total events	50		14			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.09 (P = 0.04)

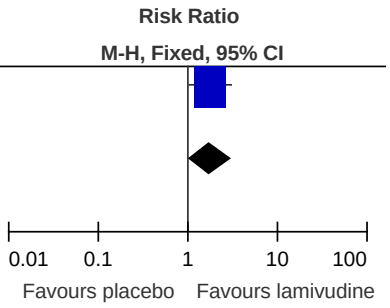


Figure 3947: Undetectable HBV DNA (<0.7meq/mL) [end of treatment- week 52)]

Study or Subgroup	Lamivudine Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jonas 2002	117	191	15	95	100.0%	3.88 [2.41, 6.26]
Total (95% CI)		**191**		**95**	**100.0%**	**3.88 [2.41, 6.26]**
Total events	117		15			

Heterogeneity: Not applicable

Test for overall effect: Z = 5.56 (P < 0.00001)

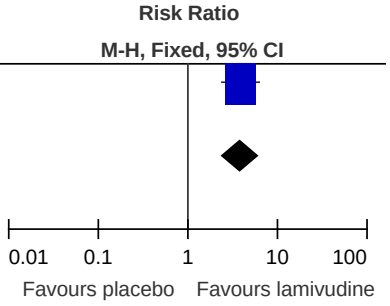


Figure 395: Loss of HBsAg [end of treatment- week 52]

Study or Subgroup	Lamivudine Events	Total	placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Jonas 2002	3	191	0	95	100.0%	4.52 [0.41, 50.35]
Total (95% CI)		**191**		**95**	**100.0%**	**4.52 [0.41, 50.35]**
Total events	3		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.23 (P = 0.22)

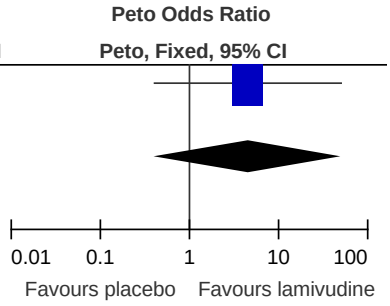
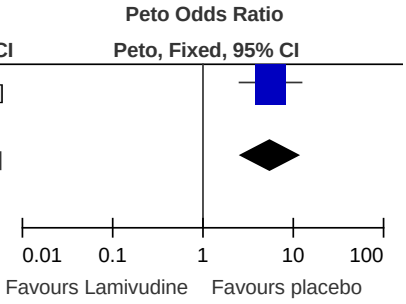


Figure 396: Incidence of resistance [end of treatment- week 52]

Study or Subgroup	Lamivudine Events	Total	placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Jonas 2002	31	166	0	86	100.0%	5.61 [2.54, 12.37]
Total (95% CI)		**166**		**86**	**100.0%**	**5.61 [2.54, 12.37]**
Total events	31		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 4.27 (P < 0.0001)



INF-α 2b + LAM (6 months) vs. INF-α 2b + LAM (12 months)

Figure 397: ALT normalization at end of therapy.

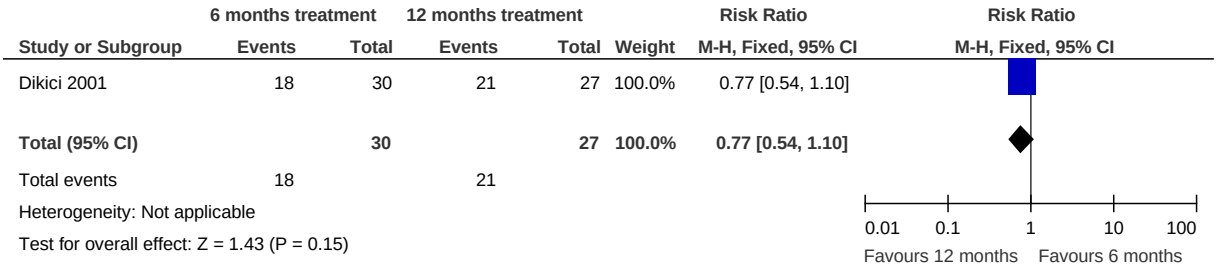


Figure 398: HBeAg clearance at end of therapy

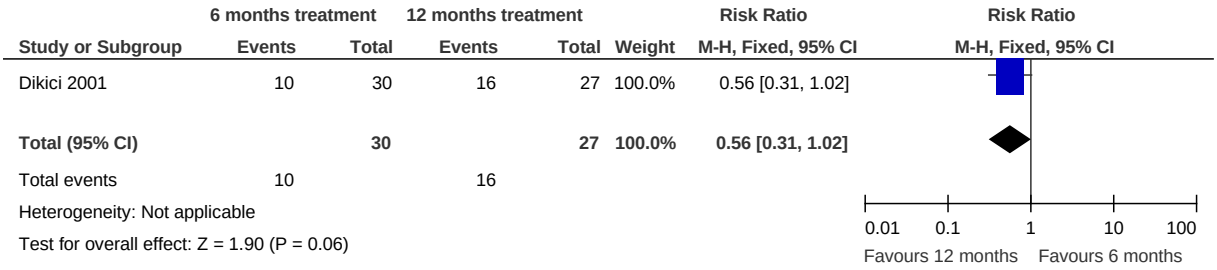


Figure 399: HBeAg seroconversion at end of therapy.

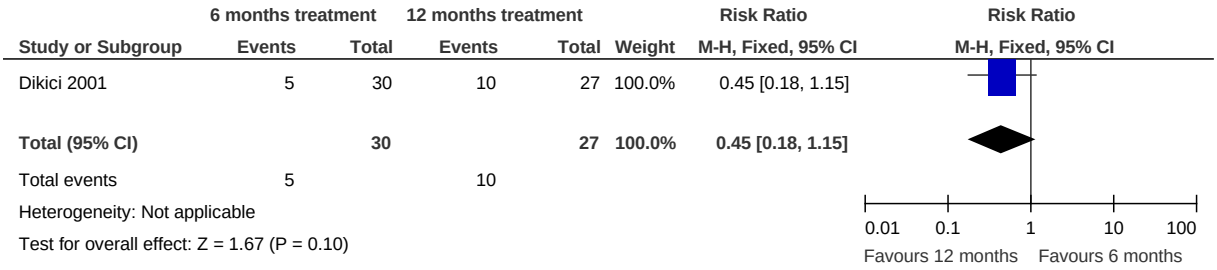


Figure 400: HBsAg clearance at end of therapy.

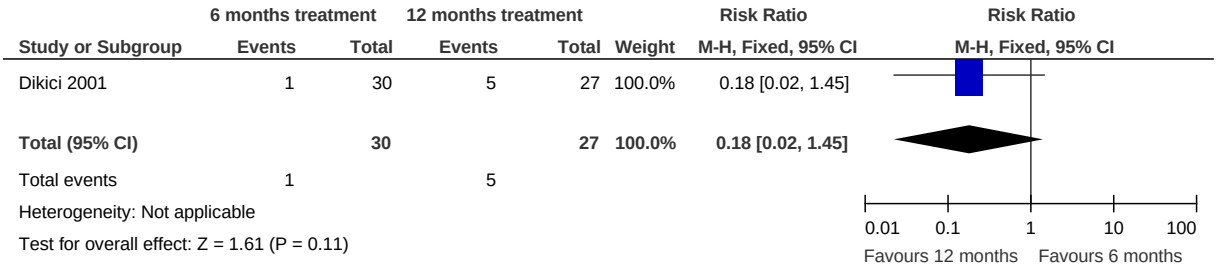


Figure 401: HBsAg seroconversion at end of therapy.

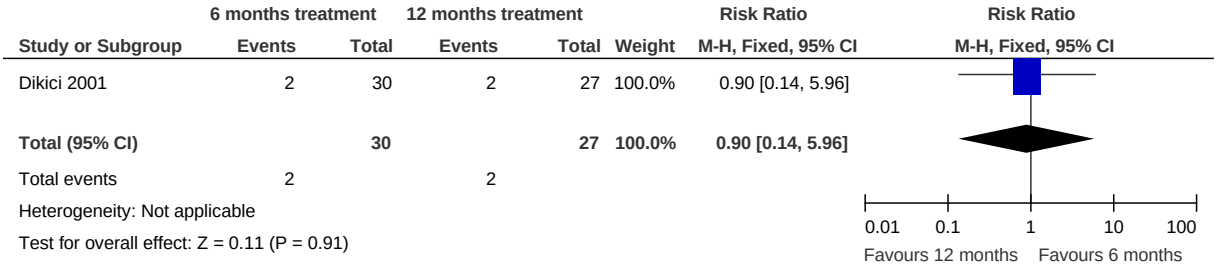


Figure 402: Undetectable HBV DNA at end of therapy

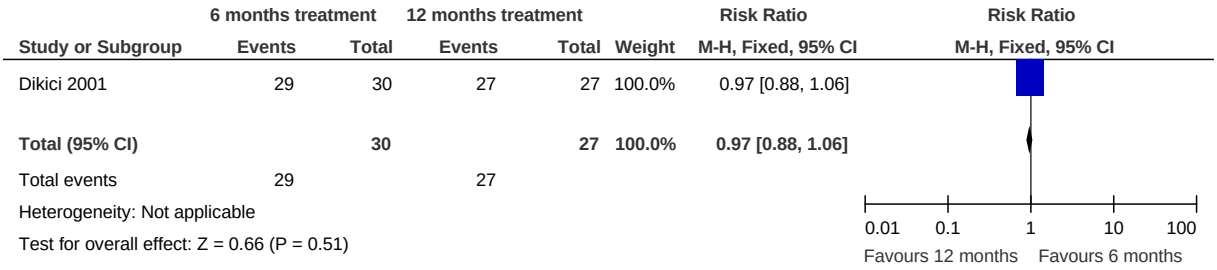


Figure 403: ALT normalization 6 months after end of therapy.

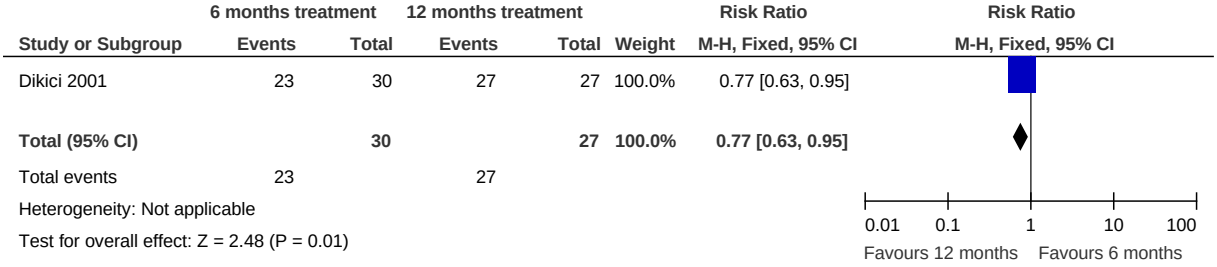


Figure 404: HBeAg clearance 6 months after end of therapy.

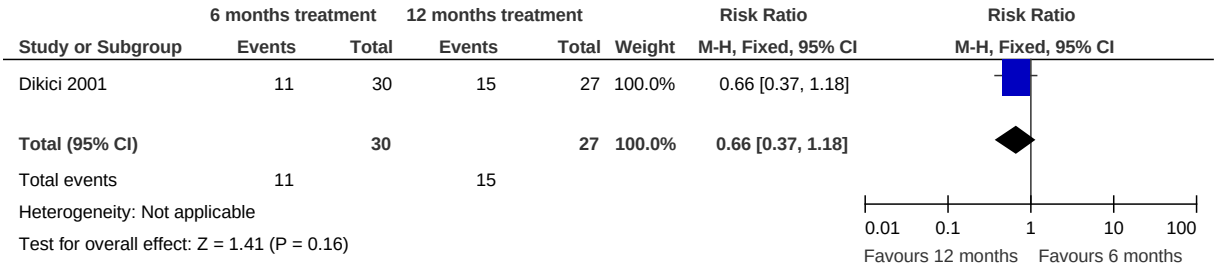


Figure 405: HBeAg seroconversion 6 months after end of therapy.

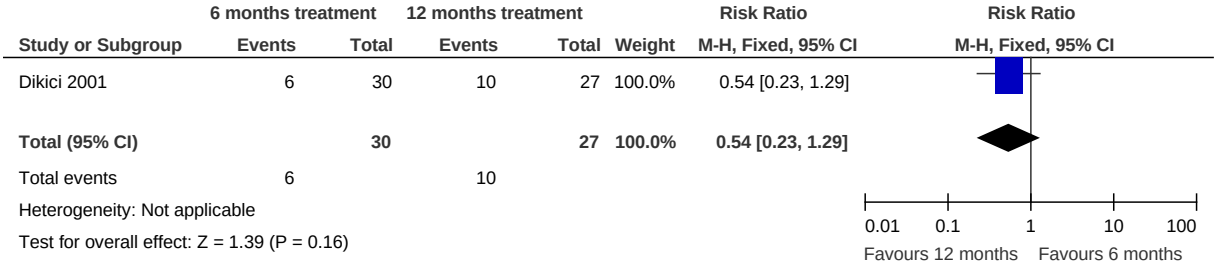


Figure 406: HBsAg clearance 6 months after end of therapy.

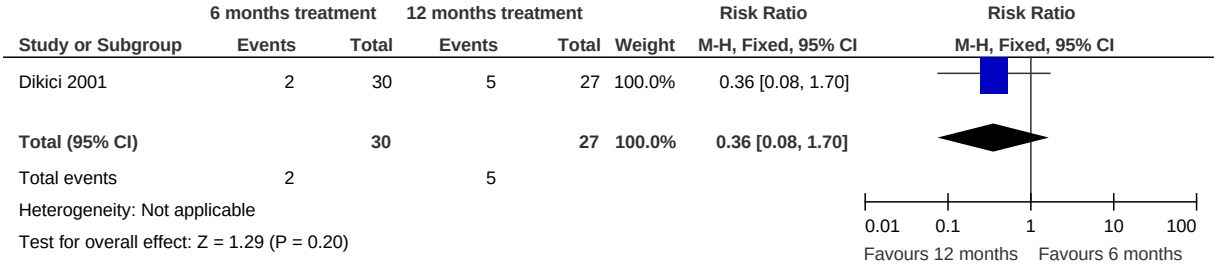


Figure 407: HBsAg seroconversion 6 months after end of therapy.

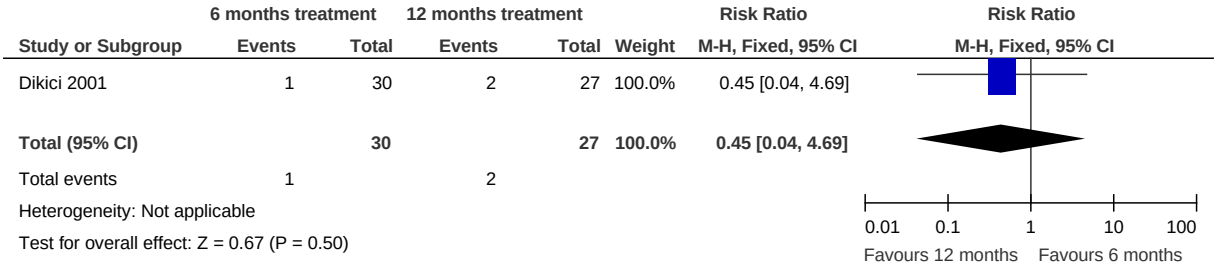
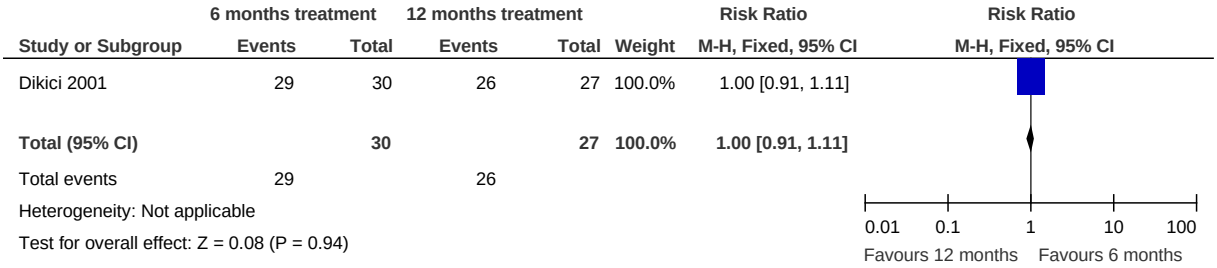


Figure 408: Undetectable HBV DNA 6 months after end of therapy.



G.3.2 Sequential therapy

G.3.2.1 Sequential antiviral therapy for HBeAg (+) adults with CHB

Lamivudine followed by pegylated interferon alpha-2b versus placebo followed by pegylated interferon alpha-2b

Figure 409: % of patients with undetectable HBV DNA (<4700 copies/ml) (assessed at end of 28 weeks treatment)

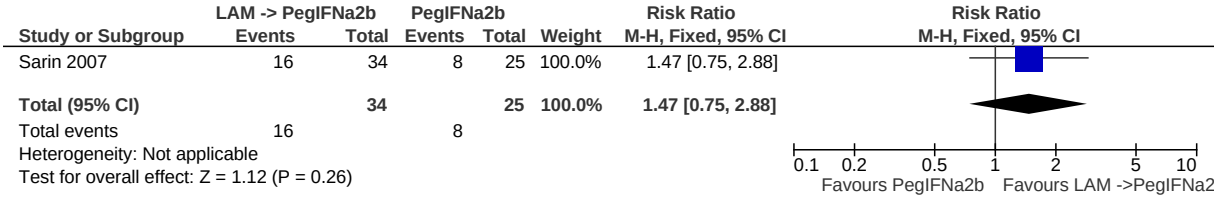


Figure 410: % of patients with undetectable HBV DNA (<4,700 copies/ml) (assessed at 24 weeks follow up)

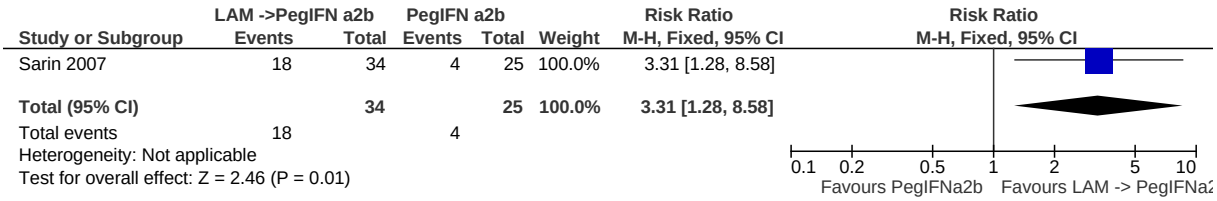


Figure 411: % of patients with HBeAg loss (assessed at end of 28 weeks treatment)

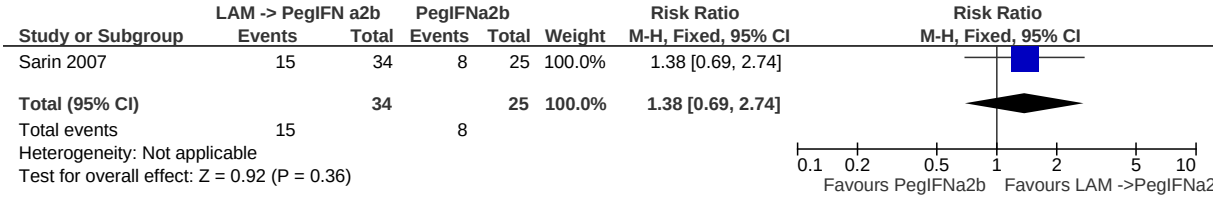


Figure 412: % of patients with HBeAg loss (assessed at 24 weeks follow up)

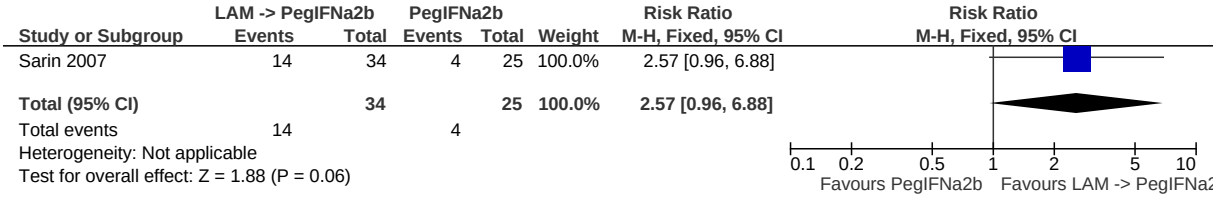


Figure 413: % of patients with ALT normalisation (assessed at end of 28 weeks treatment)

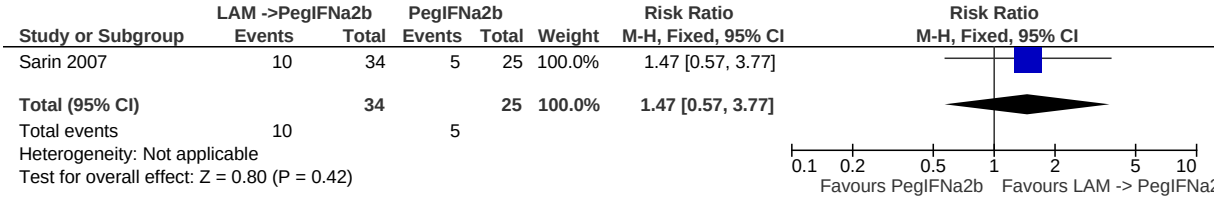
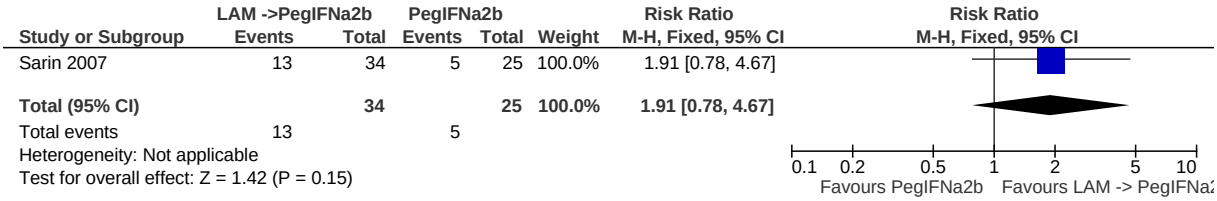


Figure 414: % of patients with ALT normalisation (assessed at 24 weeks follow up)



Switching from lamivudine to lamivudine plus interferon alpha combination therapy versus lamivudine monotherapy

Figure 415: % of patients with undetectable HBV DNA (<1.4x10^{5}copies/mL) (assessed at the end of 52 weeks treatment)

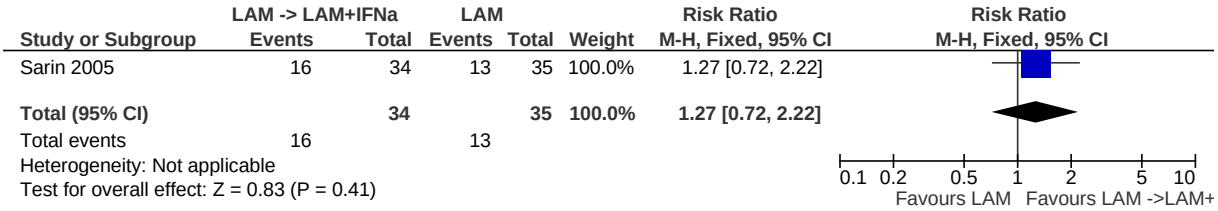


Figure 416: % of patients with ALT normalisation (assessed at the end of 52 weeks treatment)

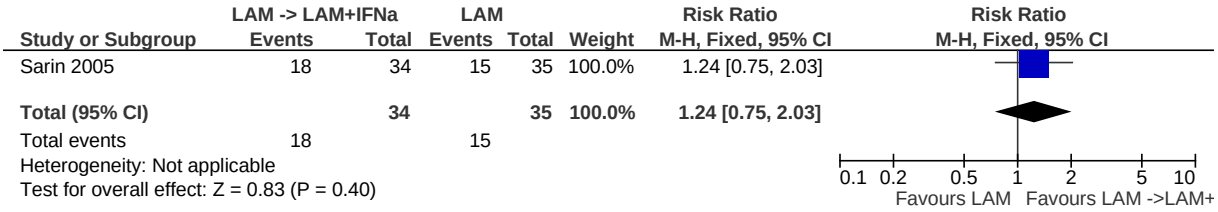


Figure 417: % of patients with HBeAg loss (assessed at the end of 52 weeks treatment)

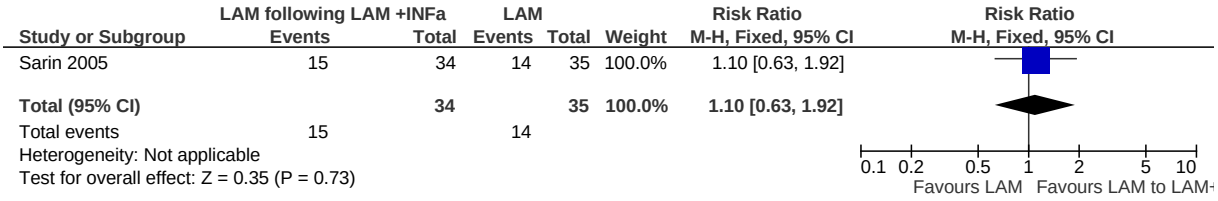


Figure 418: % of patients with HBeAg seroconversion (assessed at the end of 52 weeks treatment)

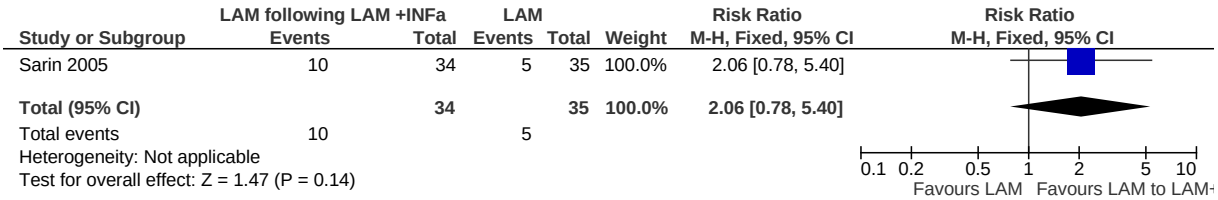


Figure 419: % of patients with histological improvement (at least 2 point reduction in the HAI score) (assessed at the end of 52 weeks treatment)

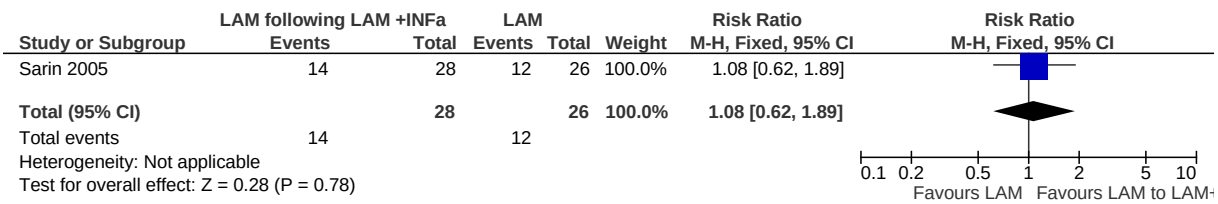


Figure 420: Incidence of resistance (YMDD mutation)

Study or Subgroup	LAM -> LAM +IFNa Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 2005	6	34	3	35	100.0%	2.06 [0.56, 7.58]
Total (95% CI)		**34**		**35**	**100.0%**	**2.06 [0.56, 7.58]**
Total events	6		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)

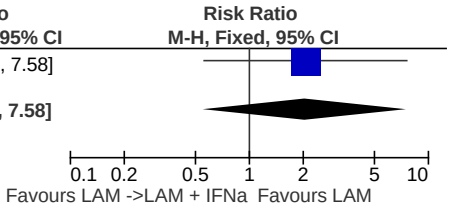


Figure 421: % of patients with undetectable HBV DNA (<1.4x10^{5}copies/mL) (assessed at 24 weeks follow up)

Study or Subgroup	LAM -> LAM +IFNa Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 2005	15	34	6	35	100.0%	2.57 [1.13, 5.85]
Total (95% CI)		**34**		**35**	**100.0%**	**2.57 [1.13, 5.85]**
Total events	15		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.26 (P = 0.02)

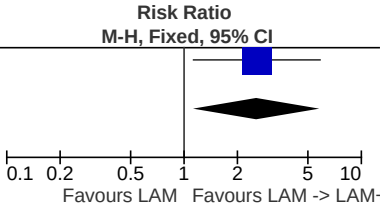


Figure 422: % of patients with ALT normalization (assessed at 24 weeks follow up)

Study or Subgroup	LAM following LAM +INFa Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 2005	15	34	5	35	100.0%	3.09 [1.26, 7.56]
Total (95% CI)		**34**		**35**	**100.0%**	**3.09 [1.26, 7.56]**
Total events	15		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.47 (P = 0.01)

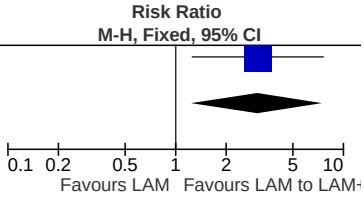


Figure 423: % of patients with HBeAg loss (assessed at 24 weeks follow up)

Study or Subgroup	LAM following LAM +INFa Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 2005	17	34	7	35	100.0%	2.50 [1.19, 5.26]
Total (95% CI)		**34**		**35**	**100.0%**	**2.50 [1.19, 5.26]**
Total events	17		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.42 (P = 0.02)

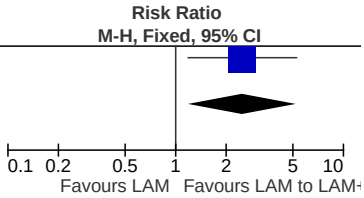


Figure 424: % of patients with HBeAg seroconversion (assessed at 24 weeks follow up)

Study or Subgroup	LAM following LAM +INFa Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sarin 2005	15	34	4	35	100.0%	3.86 [1.42, 10.46]
Total (95% CI)		**34**		**35**	**100.0%**	**3.86 [1.42, 10.46]**
Total events	15		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.66 (P = 0.008)

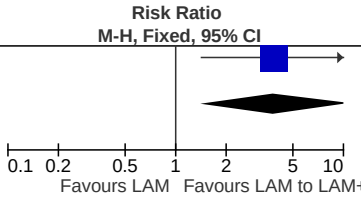
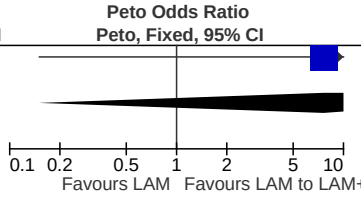


Figure 425: % of patients with HBsAg loss (assessed at 24 weeks follow up)

Study or Subgroup	LAM following LAM +INFa Events	Total	LAM Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Sarin 2005	1	34	0	35	100.0%	7.61 [0.15, 383.66]
Total (95% CI)		**34**		**35**	**100.0%**	**7.61 [0.15, 383.66]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)



Lamivudine for 8 weeks then 16 weeks of lamivudine 100mg daily + interferon α versus Lamivudine monotherapy; mixed population: HBeAg (+) and (-) (largely positive; 99%); not treated with IFN or antiviral in the last 6 months

Figure 426: % of patients with HBeAg seroconversion at end treatment week 52.

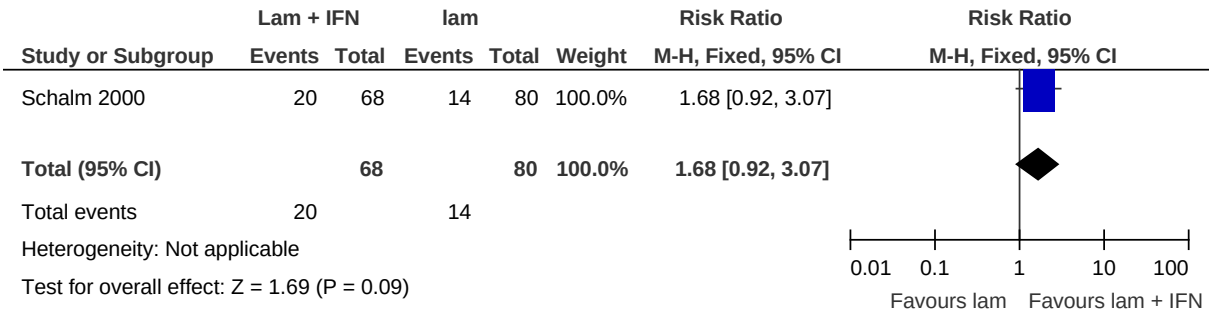


Figure 427: % of patients with HBeAg seroconversion at 12 week follow up.

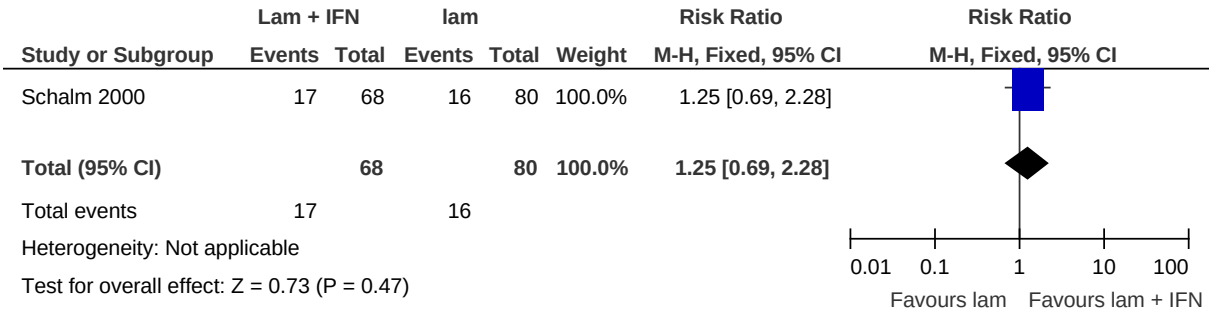


Figure 428: Histological response at end treatment week 52.

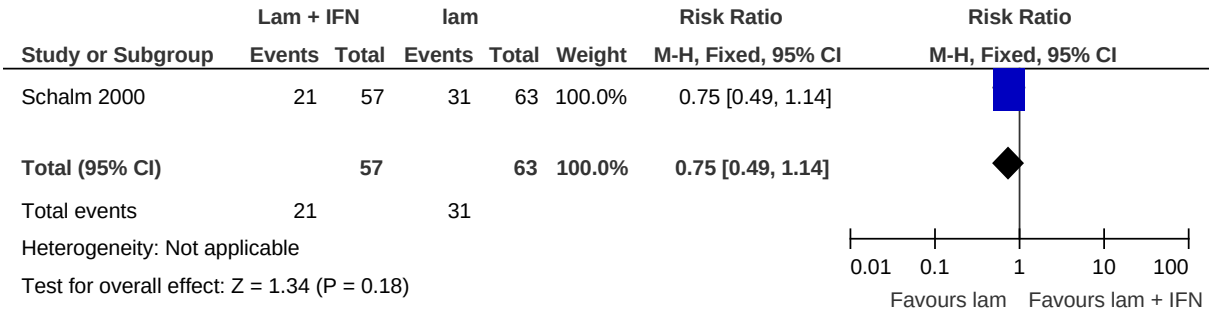


Figure 429: % of patients with HBeAg loss at end treatment week 52.

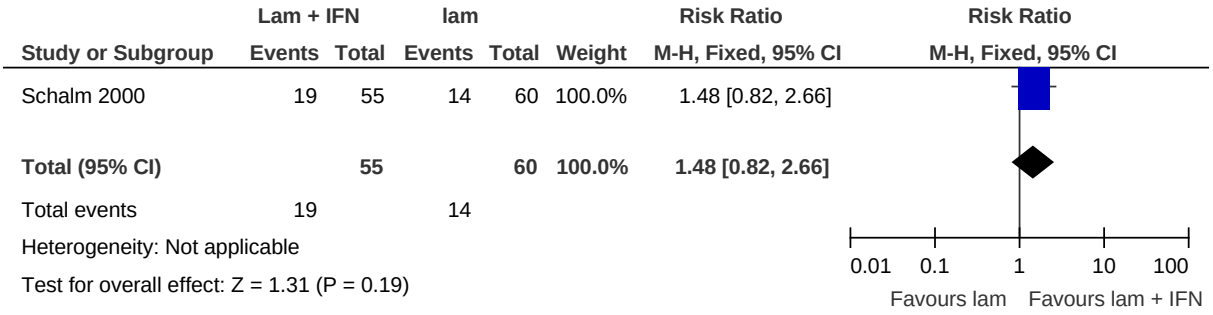


Figure 430: % of patients with HBeAg loss at 12 week follow up.

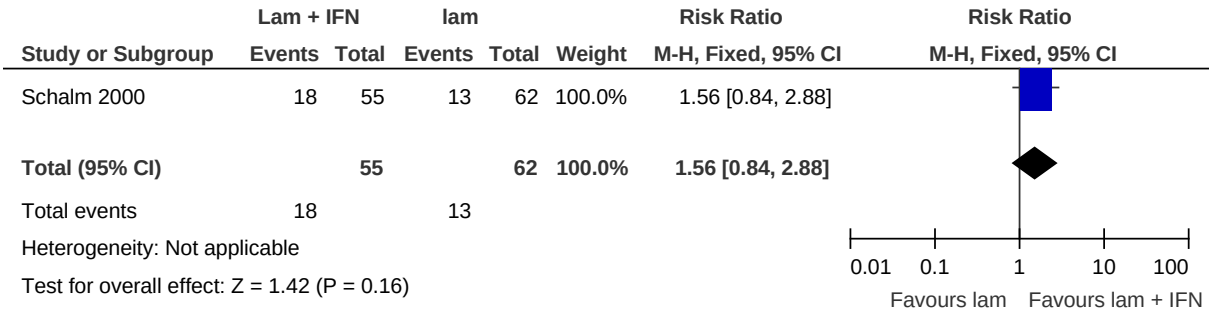


Figure 431: Undetectable HBV DNA (<3pg/mL) at end treatment week 52

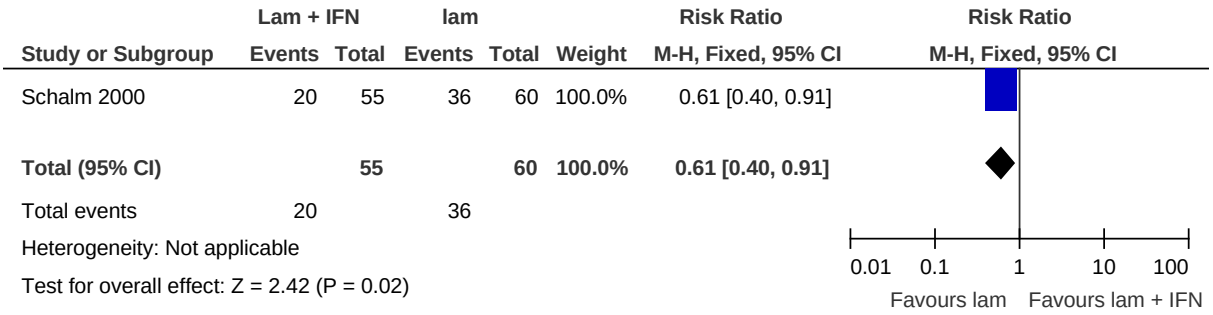


Figure 432: Undetectable HBV DNA (<3pg/mL) at 12 week follow up.

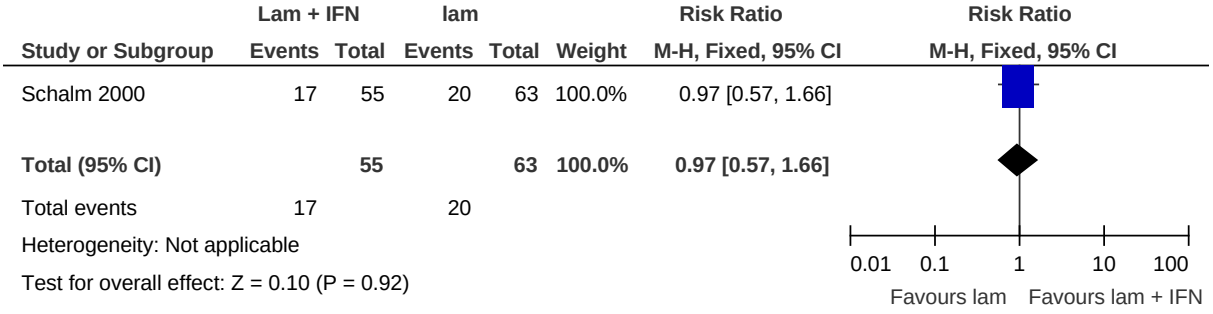


Figure 433: ALT normalisation at end treatment week 52

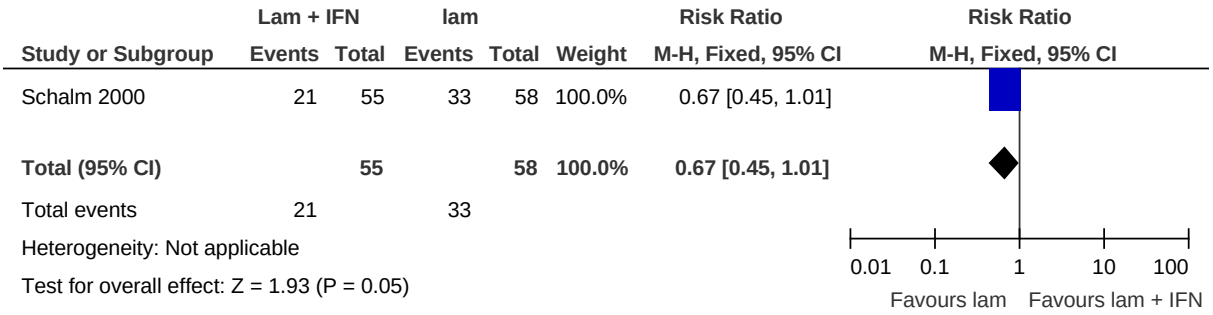


Figure 434: ALT normalisation at 12 week follow up

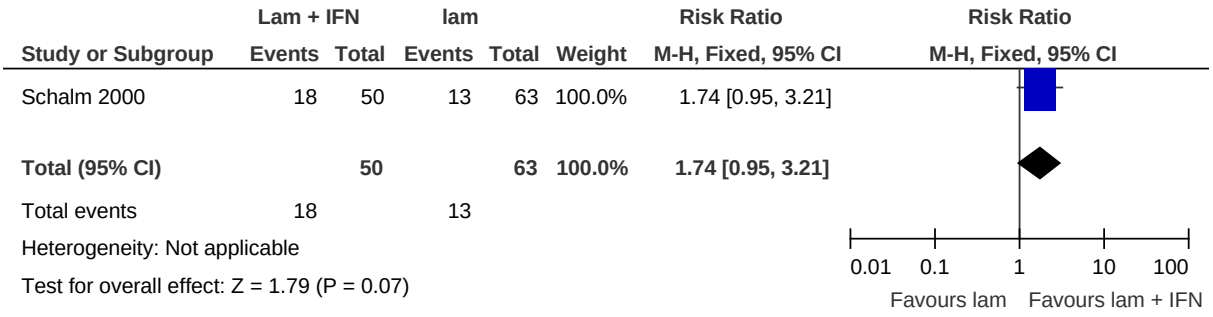


Figure 435: Genetic resistance at end treatment week 52

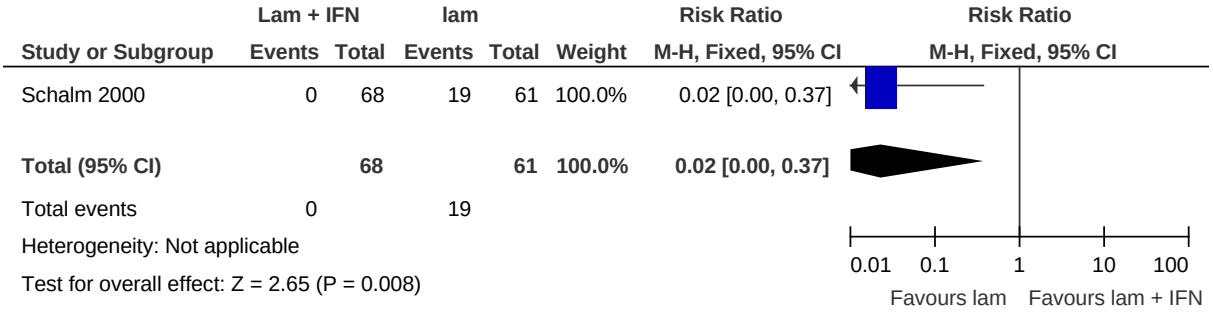


Figure 436: Genetic resistance at 12 week follow up.

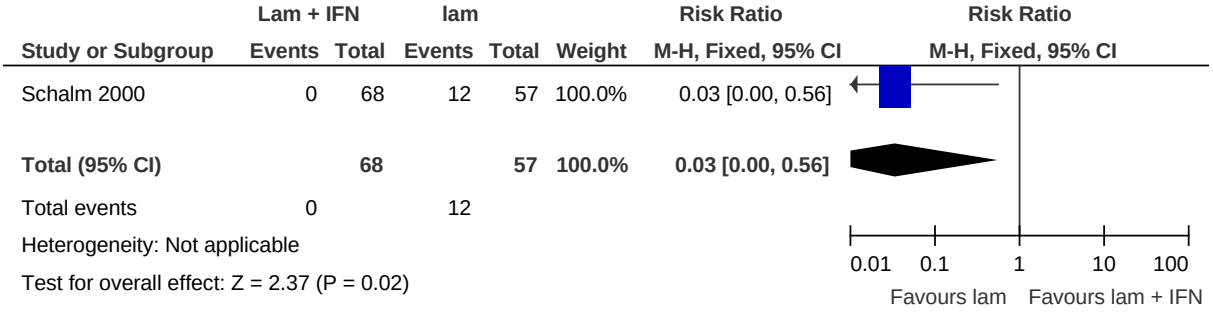
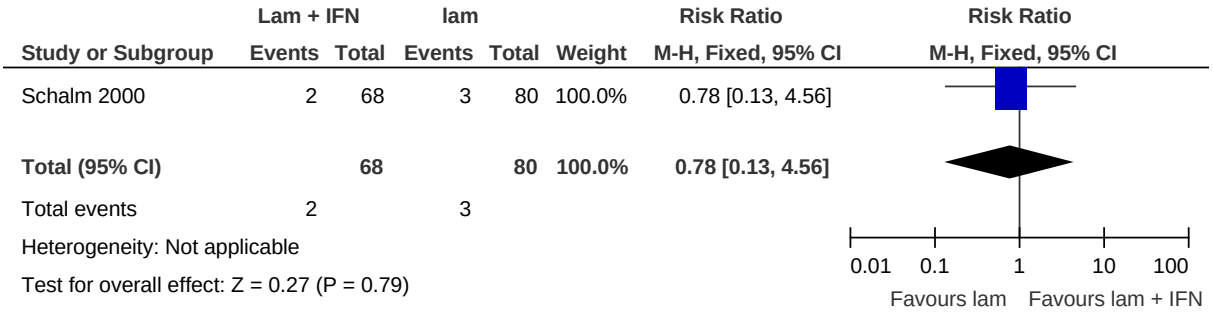


Figure 437: Adverse events leading to withdrawal.



Lamivudine for 8 weeks then 16 weeks of lamivudine 100mg daily + interferon α versus interferon α monotherapy; mixed population: HBeAg (+) and (-) (largely positive; 99%); not treated with IFN or antiviral in the last 6 months

Figure 438: of patients with HBeAg seroconversion at end treatment week 52

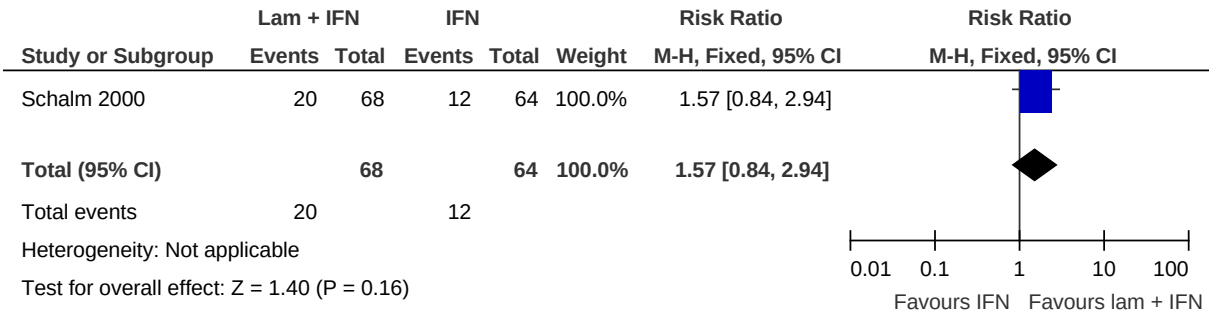


Figure 439: % of patients with HBeAg seroconversion at 12 week follow up.

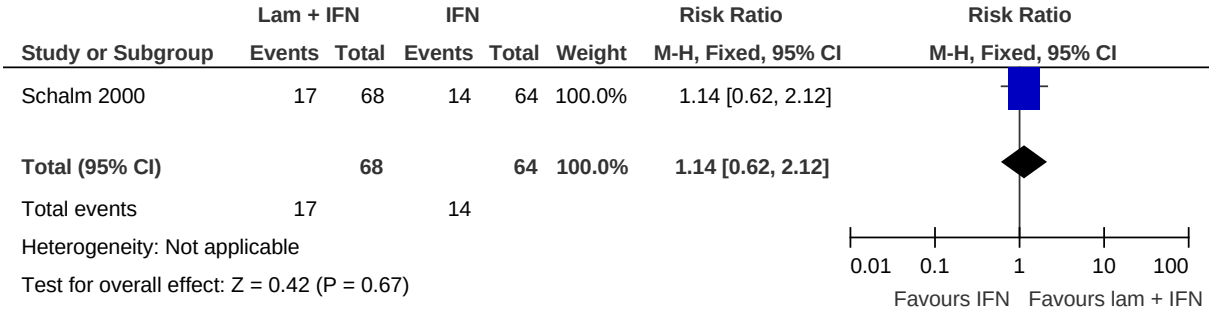


Figure 440: Histological response at end treatment week 52.

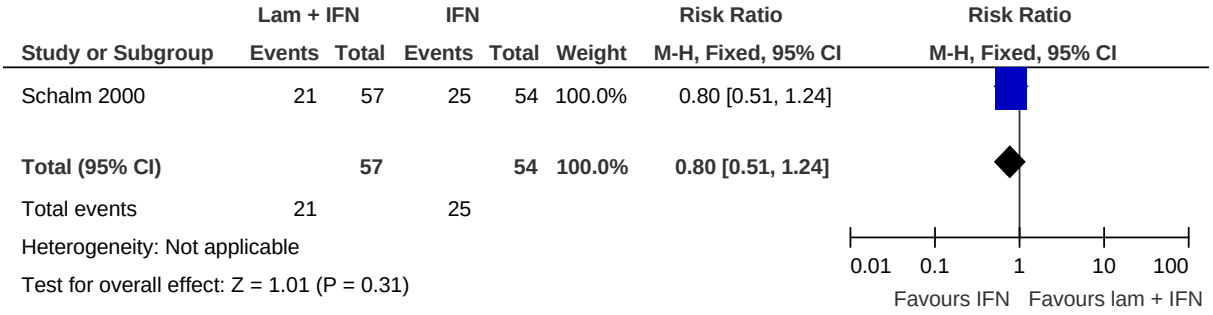


Figure 441: % of patients with HBeAg loss at end treatment week 52.

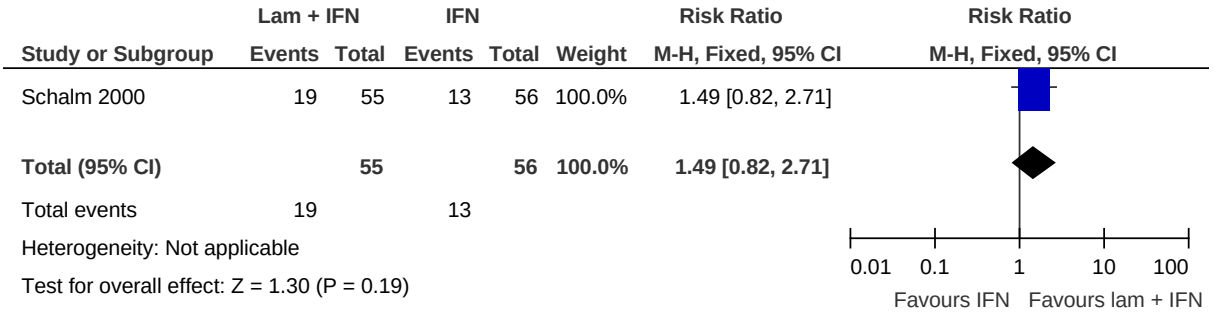


Figure 442: % of patients with HBeAg loss at 12 week follow up

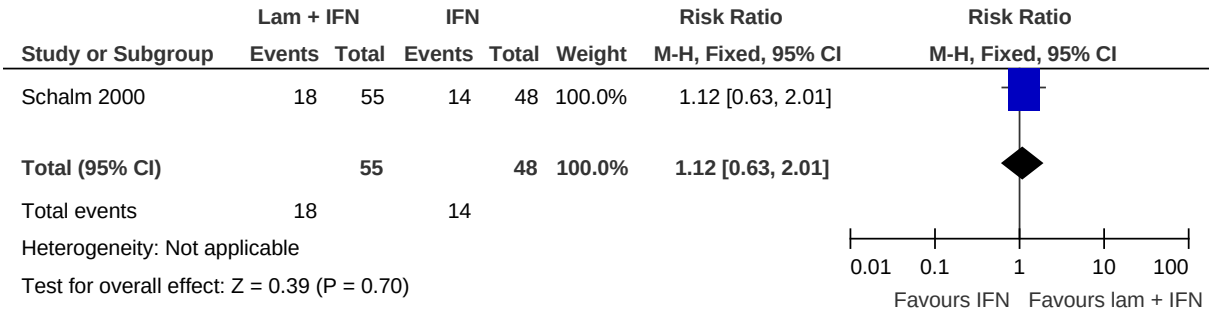


Figure 443: Undetectable HBV DNA (<3pg/mL) at end treatment week 52.

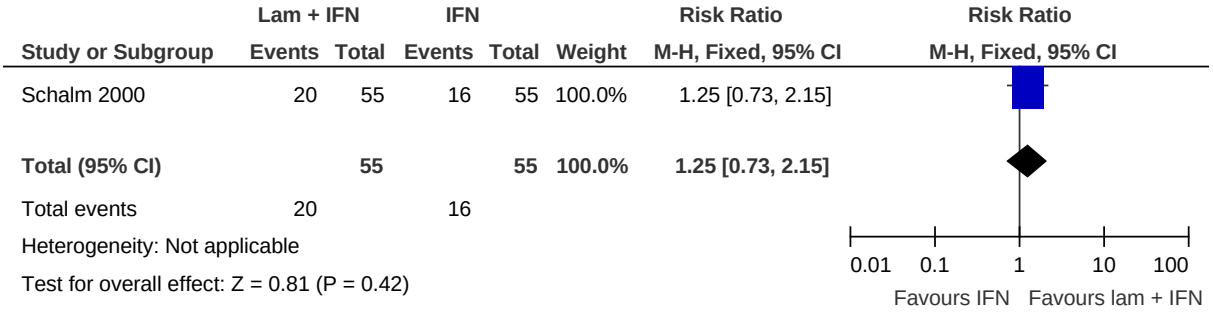


Figure 444: Undetectable HBV DNA (<3pg/mL) at 12 week follow up.

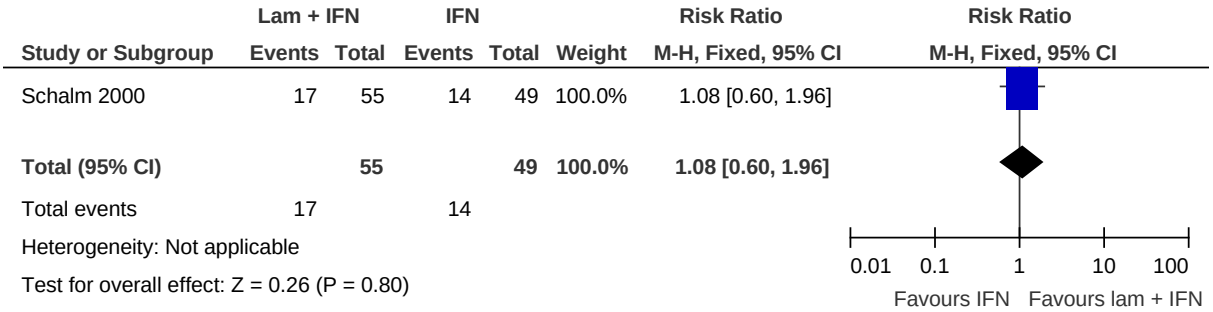


Figure 445: ALT normalisation at end treatment week 52.

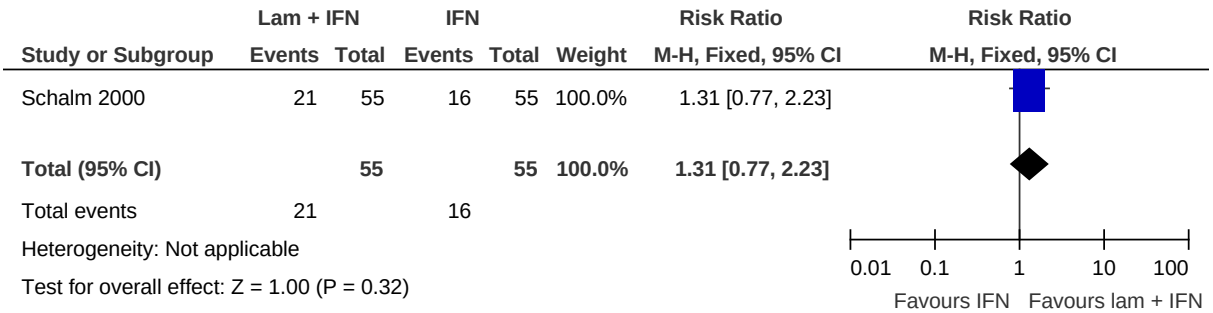


Figure 446: ALT normalisation at 12 week follow up

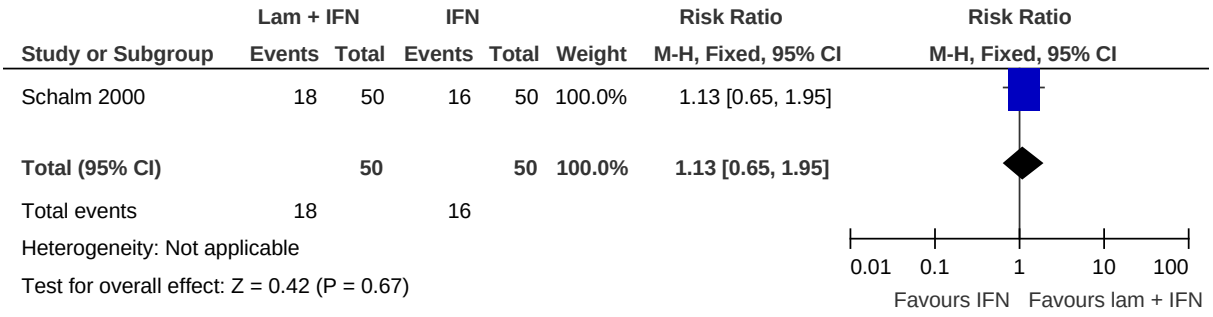
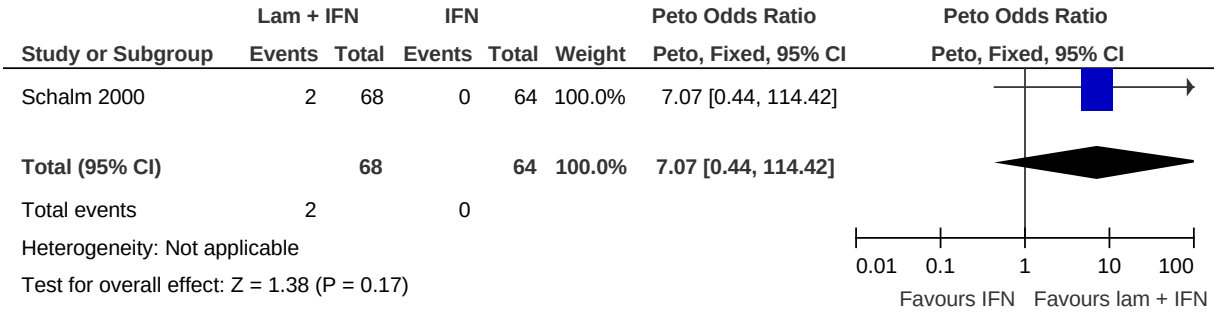


Figure 447: Adverse events leading to withdrawal.



Adefovir then telbivudine versus telbivudine

Figure 448: Undetectable HBV DNA at end of 52 weeks treatment.

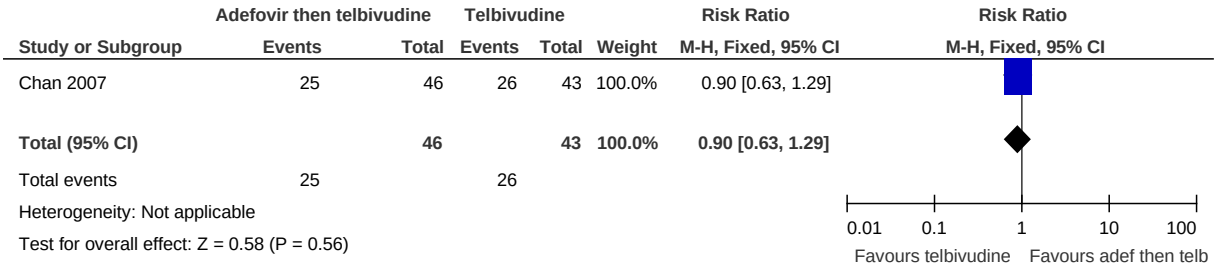


Figure 449: Viral breakthrough at end of 52 weeks treatment.

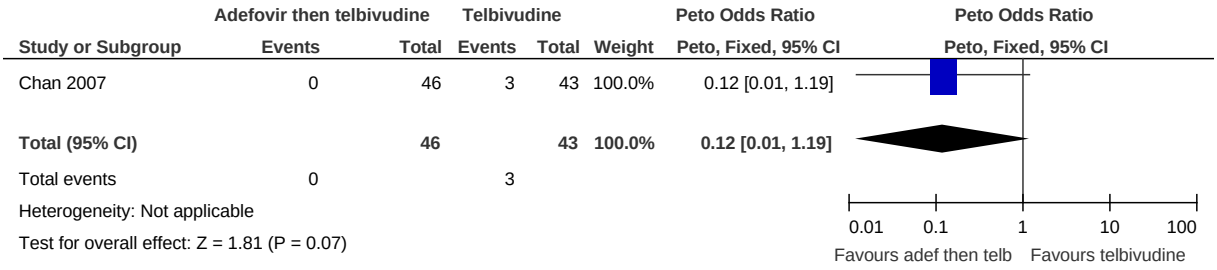


Figure 450: ALT normalisation at end of 52 weeks treatment.

Study or Subgroup	Adefovir then telbivudine Events	Total	Telbivudine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chan 2007	39	46	34	43	100.0%	1.07 [0.88, 1.31]
Total (95% CI)		**46**		**43**	**100.0%**	**1.07 [0.88, 1.31]**
Total events	39		34			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)

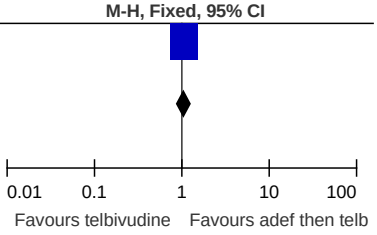


Figure 451: HBeAg loss at end of 52 weeks treatment.

Study or Subgroup	Adefovir then telbivudine Events	Total	Telbivudine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chan 2007	12	46	13	43	100.0%	0.86 [0.44, 1.68]
Total (95% CI)		**46**		**43**	**100.0%**	**0.86 [0.44, 1.68]**
Total events	12		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.66)

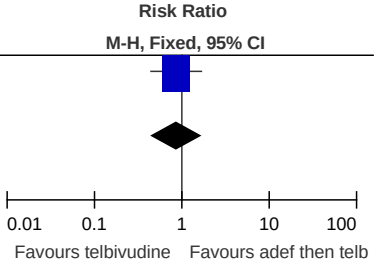
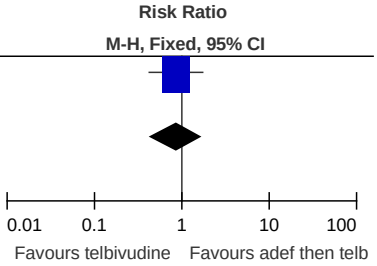


Figure 452: HBeAg seroconversion at end of 52 weeks treatment.

Study or Subgroup	Adefovir then telbivudine Events	Total	Telbivudine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chan 2007	11	46	12	43	100.0%	0.86 [0.42, 1.73]
Total (95% CI)		**46**		**43**	**100.0%**	**0.86 [0.42, 1.73]**
Total events	11		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)



Adefovir then telbivudine versus adefovir

Figure 453: Undetectable HBV DNA at end of 52 weeks treatment.

Study or Subgroup	Adefovir then telbivudine Events	Total	Adefovir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chan 2007	25	46	17	42	100.0%	1.34 [0.85, 2.11]
Total (95% CI)		**46**		**42**	**100.0%**	**1.34 [0.85, 2.11]**
Total events	25		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)

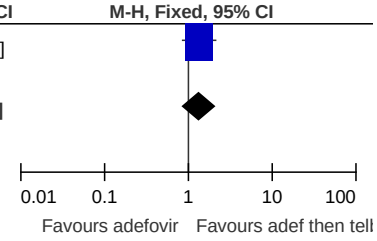


Figure 454: Viral breakthrough at end of 52 weeks treatment

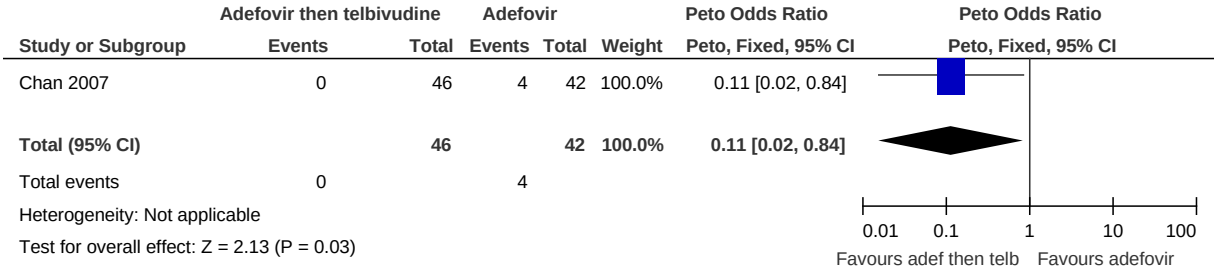


Figure 455: ALT normalisation at end of 52 weeks treatment.

Figure 456: HBeAg loss at end of 52 weeks treatment.

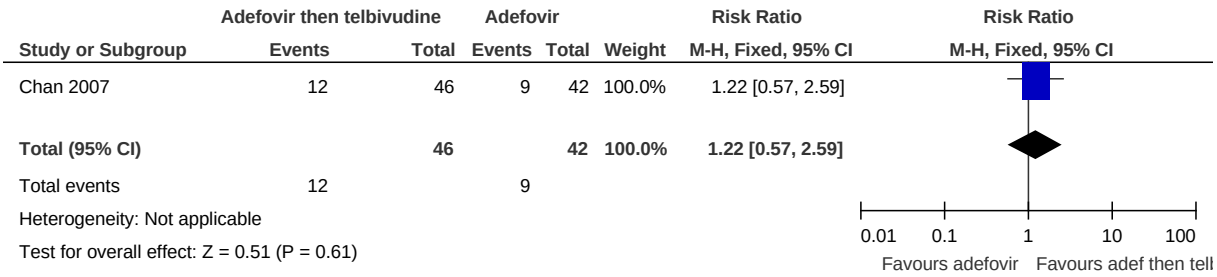


Figure 457: HBeAg seroconversion at end of 52 weeks treatment.

Interferon alpha followed by interferon alpha plus lamivudine combination therapy followed by lamivudine versus lamivudine monotherapy

Figure 458: % of patients with HBeAg seroconversion (assessed at the end of 48 weeks treatment)

Study or Subgroup	IFNa-> IFNa+ LAM ->LAM Events	Total	LAM Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hasan2003	2	31	0	29	100.0%	7.16 [0.44, 117.45]
Total (95% CI)		**31**		**29**	**100.0%**	**7.16 [0.44, 117.45]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

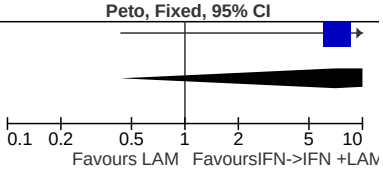


Figure 45970: % of patients with HBeAg seroconversion (assessed at 52 weeks follow up)

Study or Subgroup	IFNa-> IFNa+ LAM ->LAM Events	Total	LAM Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hasan2003	2	31	0	29	100.0%	7.16 [0.44, 117.45]
Total (95% CI)		**31**		**29**	**100.0%**	**7.16 [0.44, 117.45]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

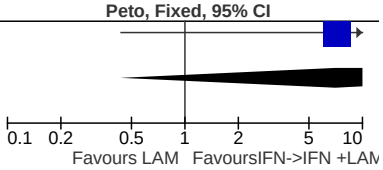


Figure 460: % of patients with ALT normalisation (assessed at the end of 48 weeks treatment)

Study or Subgroup	IFNa-> IFNa+ LAM ->LAM Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hasan2003	29	31	28	29	100.0%	0.97 [0.86, 1.09]
Total (95% CI)		**31**		**29**	**100.0%**	**0.97 [0.86, 1.09]**
Total events	29		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

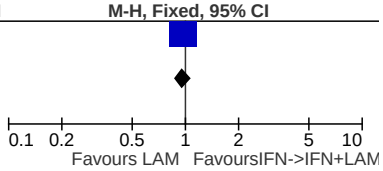


Figure 461: % of patients with ALT normalisation (assessed at 52 weeks follow up)

Study or Subgroup	IFNa-> IFNa+ LAM ->LAM Events	Total	LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hasan2003	3	31	2	29	100.0%	1.40 [0.25, 7.81]
Total (95% CI)		**31**		**29**	**100.0%**	**1.40 [0.25, 7.81]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)

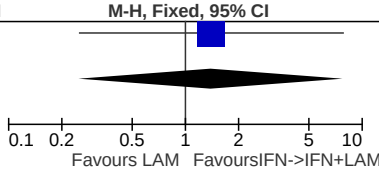
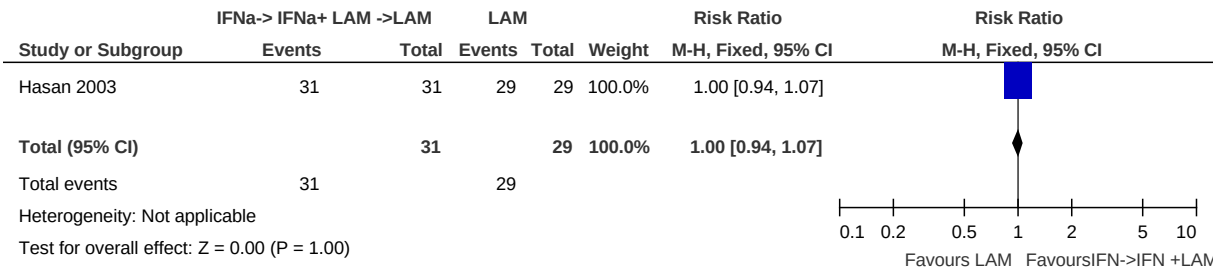


Figure 462: % of patients with undetectable HBV DNA (assessed at the end of 48 weeks treatment).



Switching from lamivudine to entecavir versus continuing lamivudine in lamivudine refractory patients

Figure 463: Log reduction in HBV DNA.

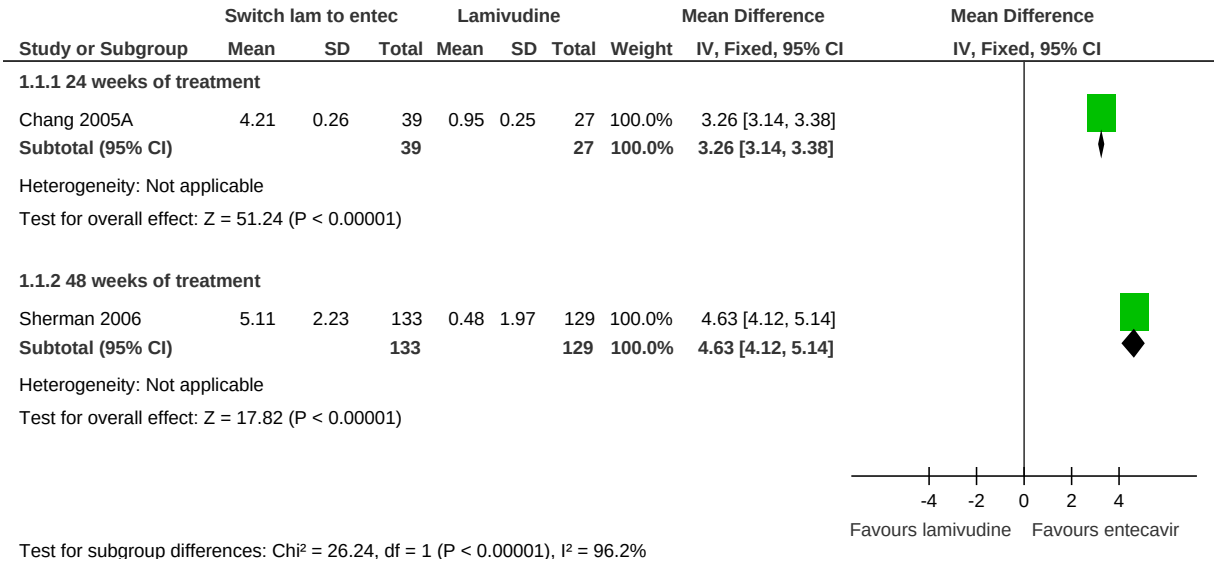


Figure 464: Undetectable HBV DNA.

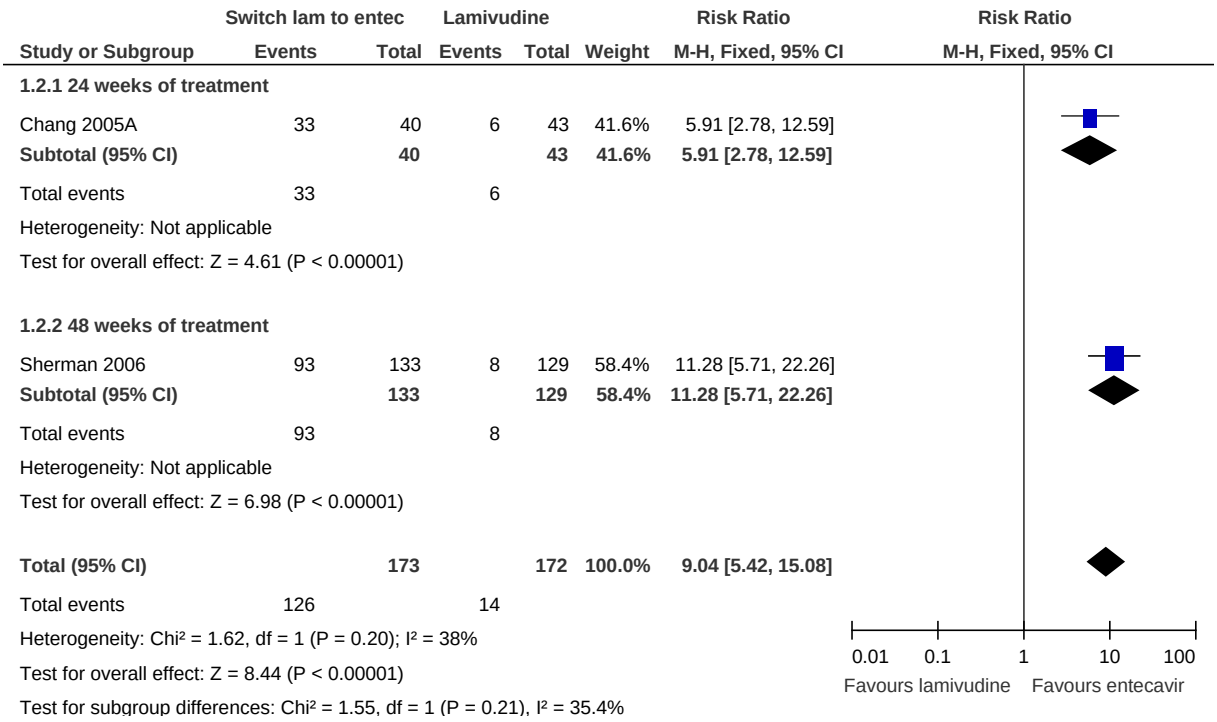


Figure 465: ALT normalisation.

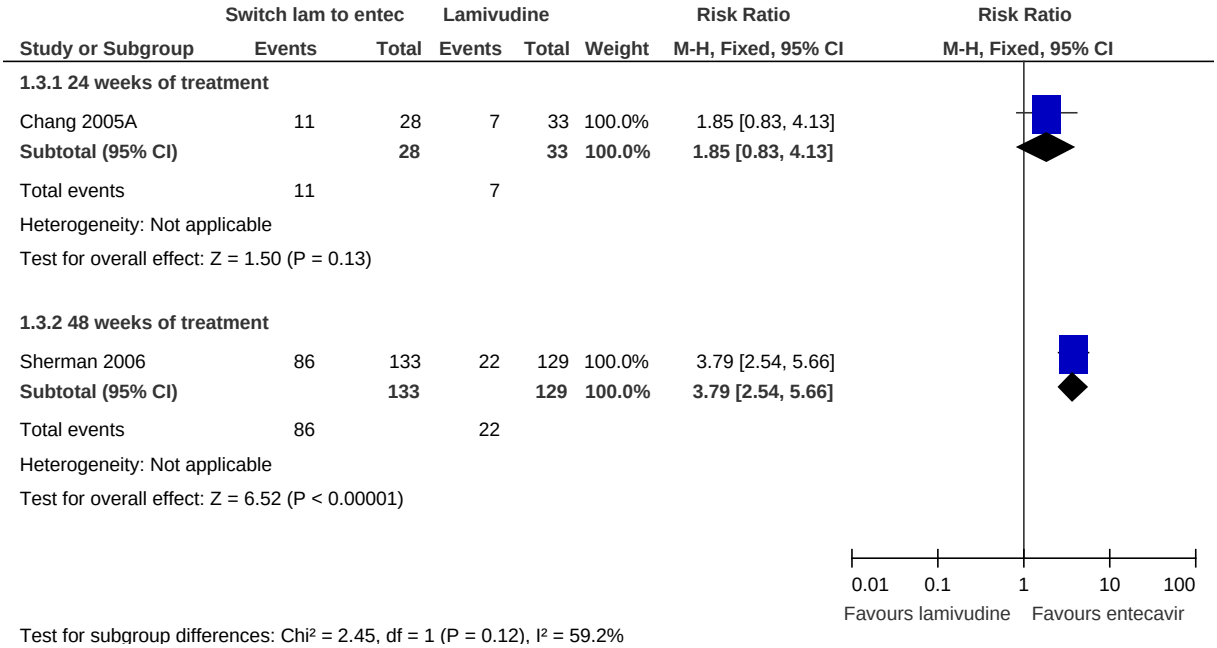


Figure 466: HBeAG loss at 48 weeks of treatment.

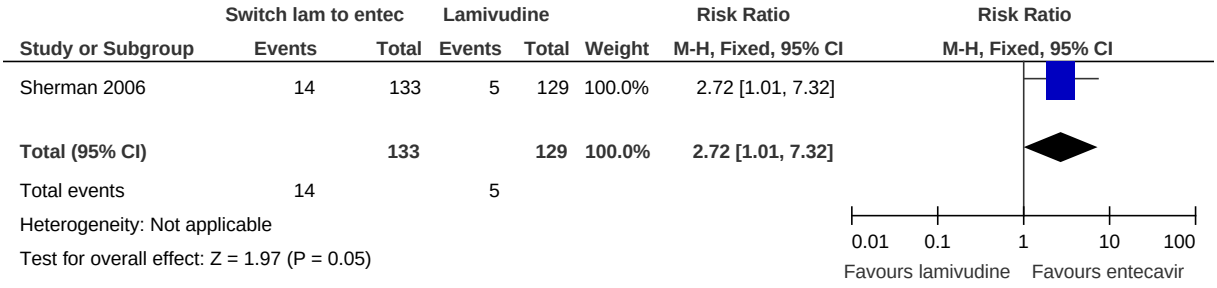


Figure 467: HBeAG seroconversion at 48 weeks of treatment

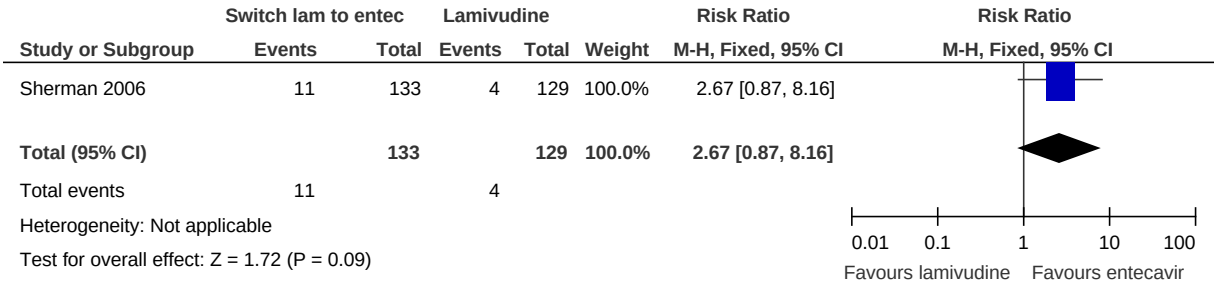


Figure 468: **Histological improvement at 48 weeks of treatment.**

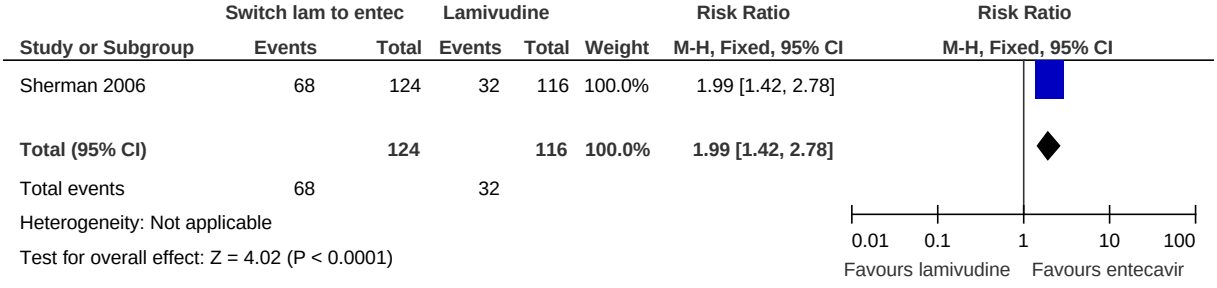
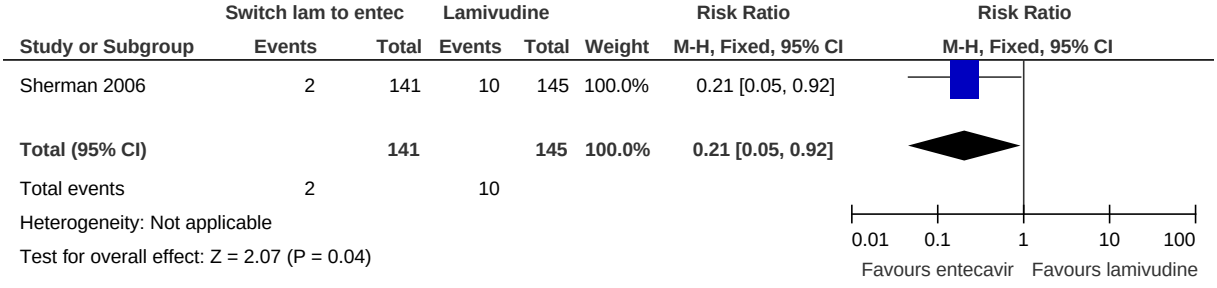


Figure 469: **Withdrawn due to adverse events at 48 weeks of treatment.**



Switching from lamivudine plus adefovir to entecavir plus adefovir versus continuing lamivudine plus adefovir in lamivudine-resistant patients

Figure 470: Reduction of HBV DNA (log 10 IU/mL) at end 52 weeks treatment.

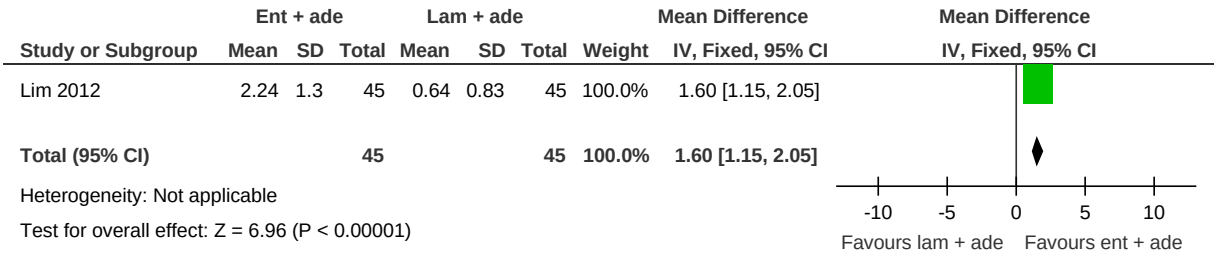


Figure 471: **Undetectable HBV DNA (60IU/mL) at end 52 weeks treatment.**

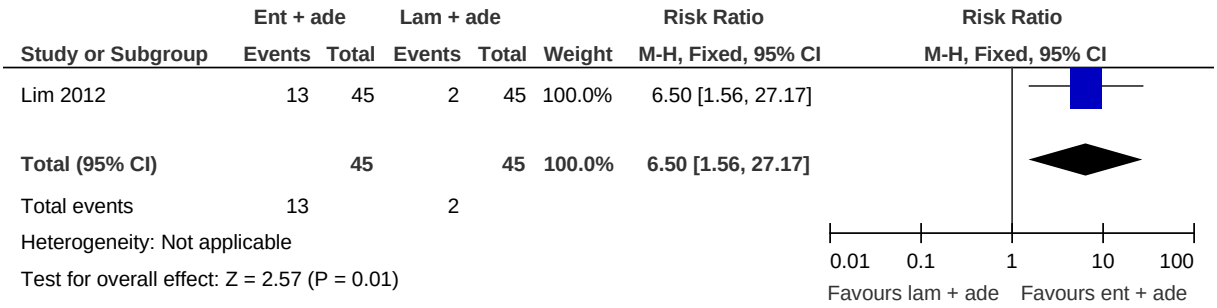


Figure 472: **Virological breakthrough at end 52 weeks treatment.**

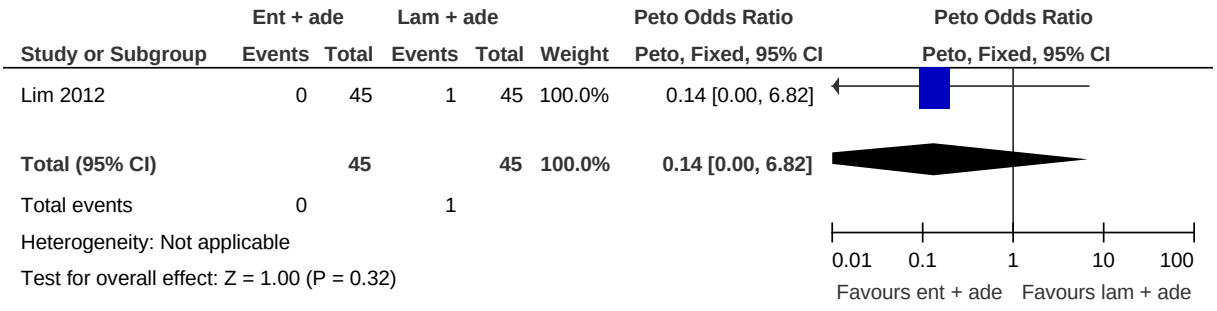


Figure 473: **Resistance mutation to entecavir or adefovir at end 52 weeks treatment.**

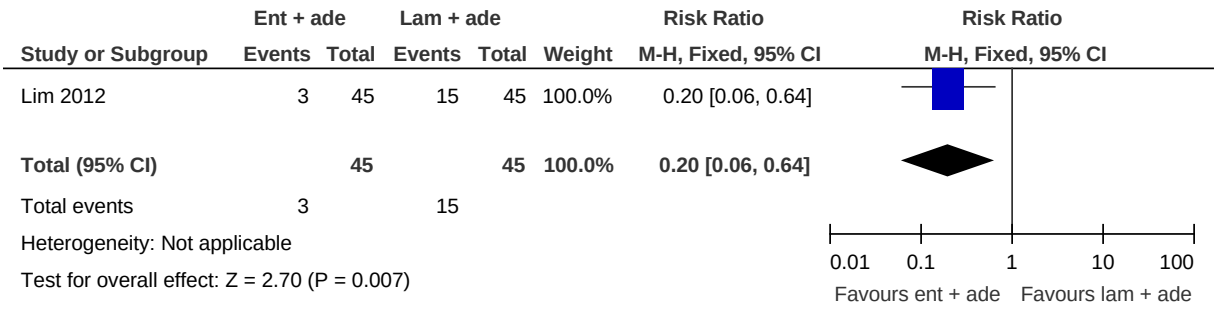


Figure 474: **ALT normalisation at end 52 weeks treatment.**

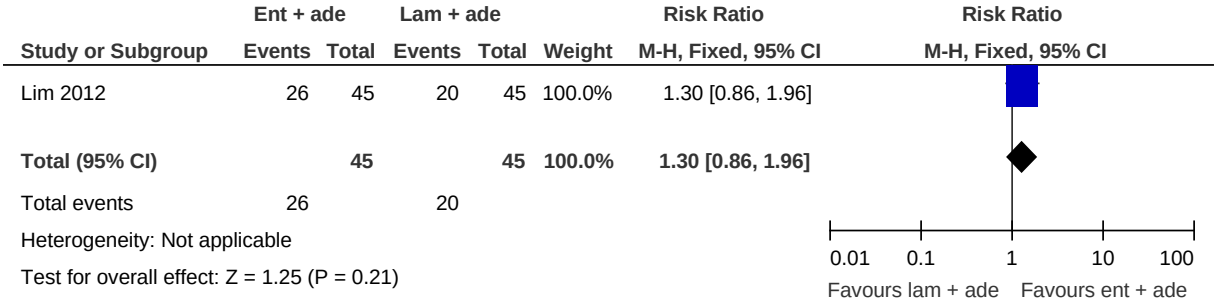
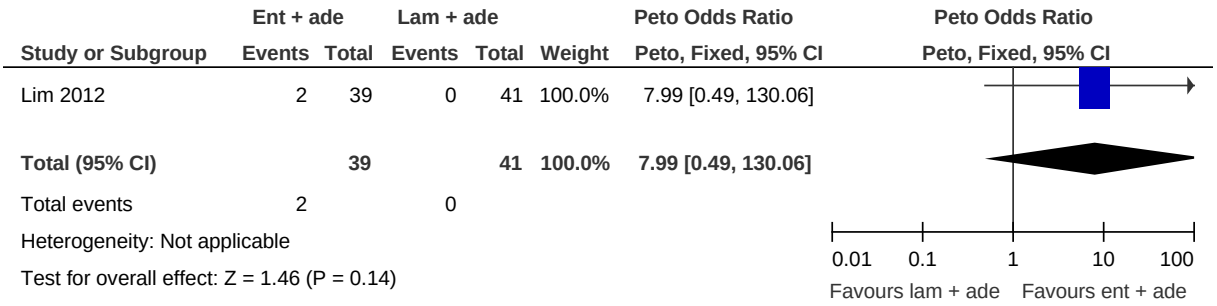


Figure 475: **HBeAg loss at end 52 weeks treatment.**



Switching from lamivudine to telbivudine versus continuing lamivudine in patients previously treated with lamivudine who had persistant viraemia

Figure 476: log reduction HBV DNA (assessed at the end of 52 weeks treatment)

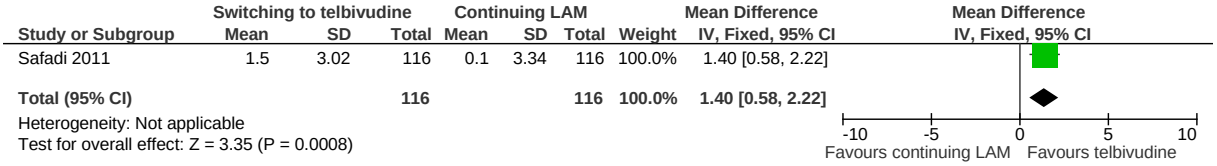


Figure 477: % of patients with undetectable HBV DNA (<300 copies/mL) (assessed at the end of 52 weeks treatment)

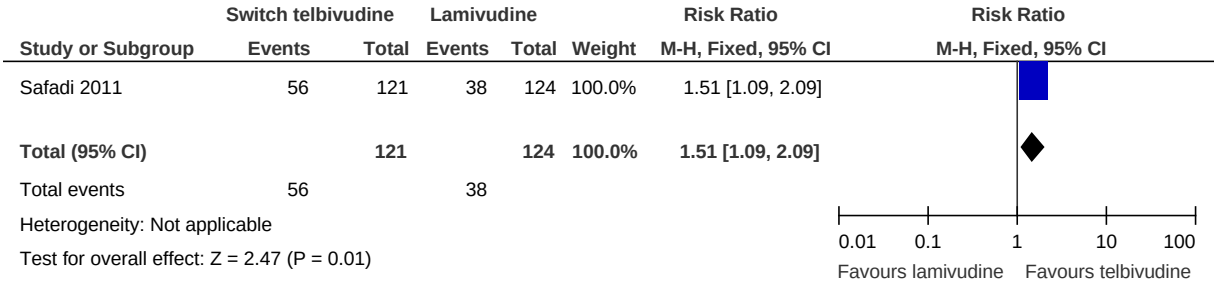


Figure 478: % of patients with HBeAg loss (assessed at the end of 52 weeks treatment)

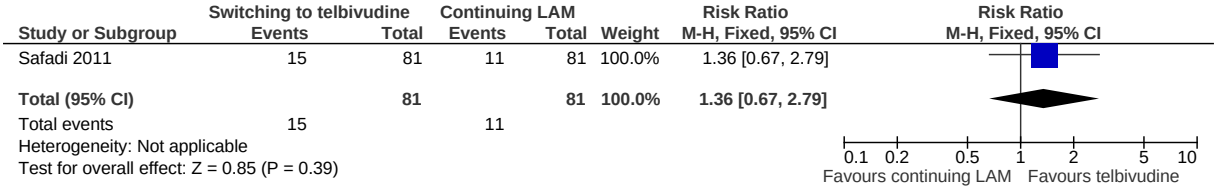


Figure 479: % of patients with HBeAg seroconversion (assessed at the end of 52 weeks treatment)

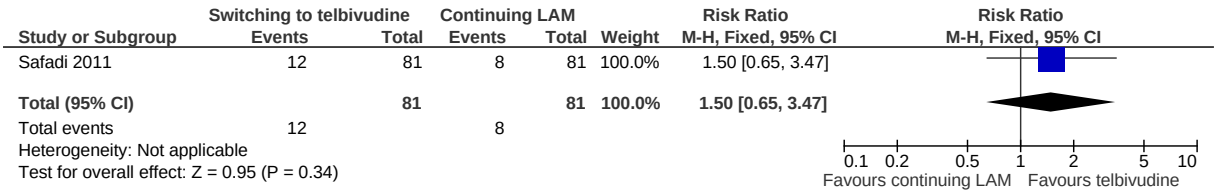


Figure 480: % of patients with ALT normalisation (assessed at the end of 52 weeks treatment)

Study or Subgroup	Switching to telbivudine Events	Total	Continuing LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Safadi 2011	32	53	27	53	100.0%	1.19 [0.84, 1.67]
Total (95% CI)		**53**		**53**	**100.0%**	**1.19 [0.84, 1.67]**
Total events	32		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

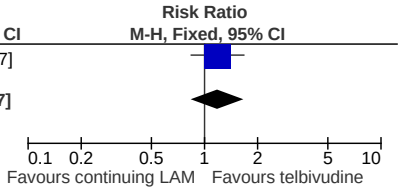


Figure 481: Resistance (YMDD mutation) (assessed at the end of 52 weeks treatment)

Study or Subgroup	Switching to telbivudine Events	Total	Continuing LAM Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 All patients						
Safadi 2011	15	101	13	124	100.0%	1.42 [0.71, 2.84]
Subtotal (95% CI)		**101**		**124**	**100.0%**	**1.42 [0.71, 2.84]**
Total events	15		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.7.2 Patients with wild type HBV at screening						
Safadi 2011	12	101	13	106	100.0%	0.97 [0.46, 2.02]
Subtotal (95% CI)		**101**		**106**	**100.0%**	**0.97 [0.46, 2.02]**
Total events	12		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						

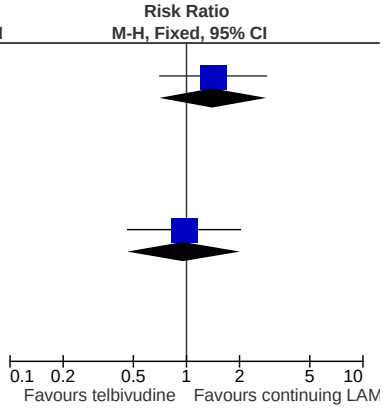
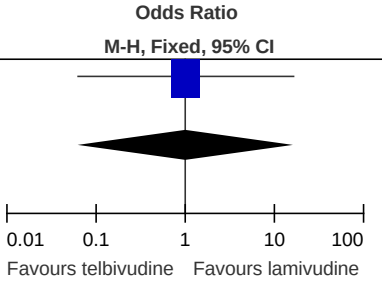


Figure 482: Withdrawn due to adverse events by end of 52 weeks treatment

.

Study or Subgroup	Switch telbivudine Events	Total	Lamivudine Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Safadi 2011	1	122	1	124	100.0%	1.02 [0.06, 16.44]
Total (95% CI)		**122**		**124**	**100.0%**	**1.02 [0.06, 16.44]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)



Switching from lamivudine to adefovir versus lamivudine plus adefovir combination therapy for HBeAg positive or negative patients previously treated with lamivudine (some resistant)

Figure 483: % of patients with undetectable HBV DNA (<160copies/mL) (assessed at end of 12 months treatment)

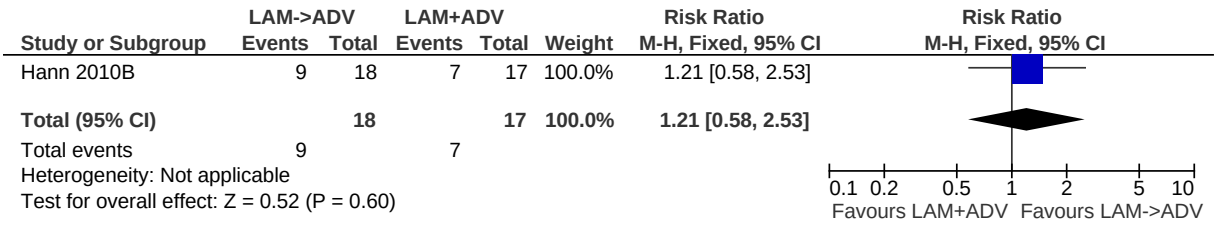
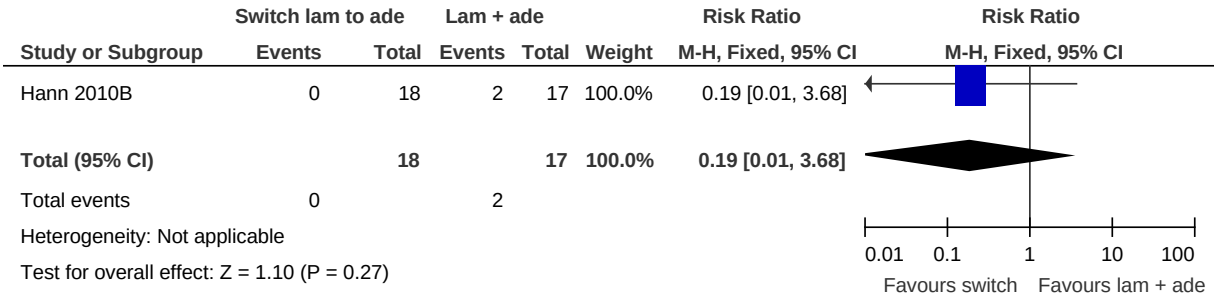


Figure 484: Viral breakthrough at 12 months treatment.



Switching from lamivudine to lamivudine plus adefovir combination therapy versus switching from lamivudine to entecavir in lamivudine resistant HBeAg positive patients

Figure 485: Log reduction HBV DNA (assessed at the end of 12 months treatment)

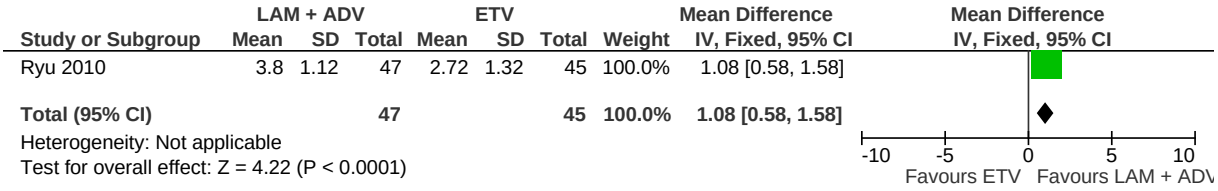


Figure 486: % of patients with undetectable HBV DNA (<300copies/mL) (assessed at the end of 12 months treatment)

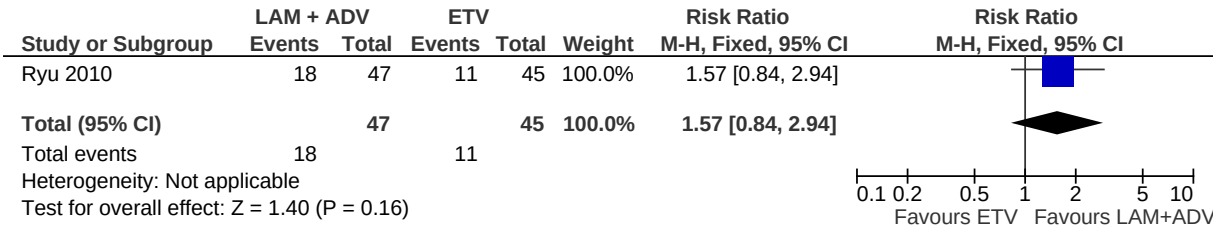


Figure 487: % of patients with ALT normalisation (assessed at the end of 12 months treatment)

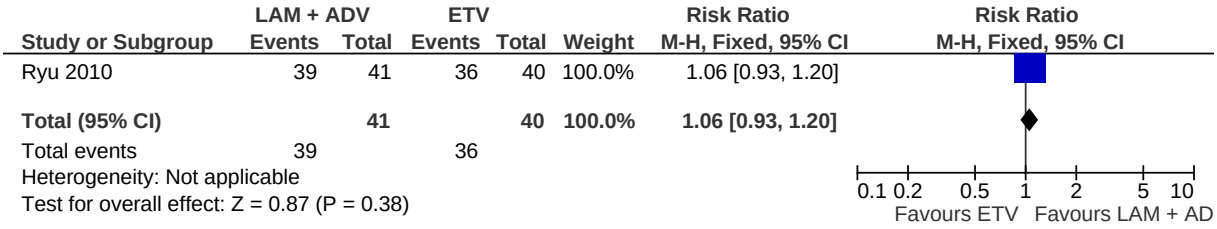


Figure 488: % of patients with HBeAg loss (assessed at the end of 12 months treatment)

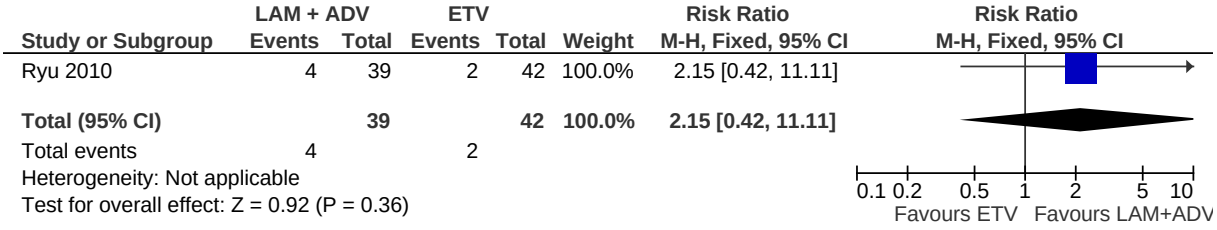


Figure 489: % of patients with HBeAg seroconversion (assessed at the end of 12 months treatment)

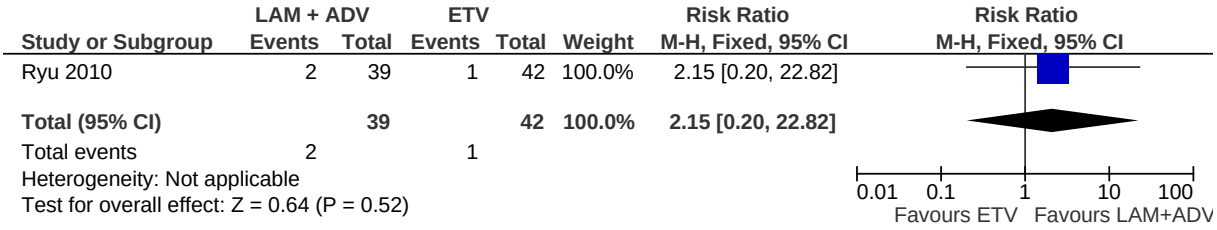
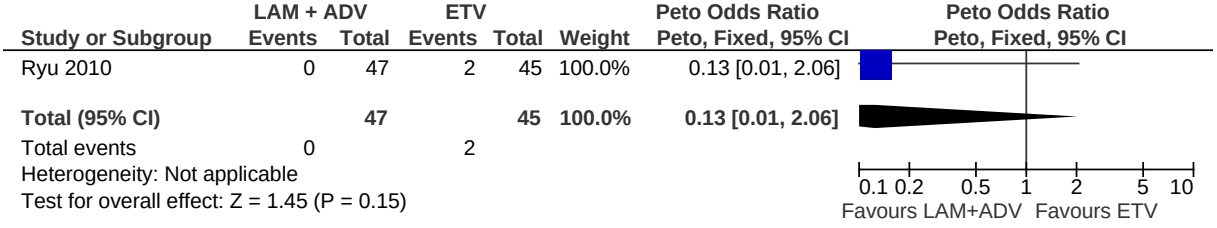


Figure 490: Incidence of genotypic resistance



G.3.2.2 Sequential antiviral therapy for HBeAg (-) adults with CHB

Switching from lamivudine plus interferon alpha-2b versus lamivudine for antiviral treatment naïve adults

Figure 491: % of patients with ALT normalization (end of 24 weeks treatment)

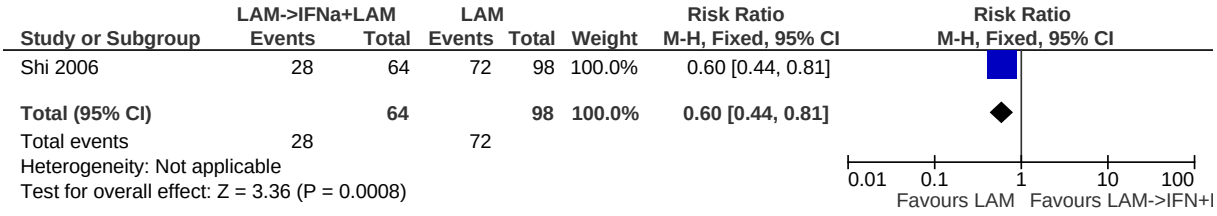


Figure 492: % of patients with undetectable HBV DNA (<1,000copies/ml) (end of 24 weeks treatment)

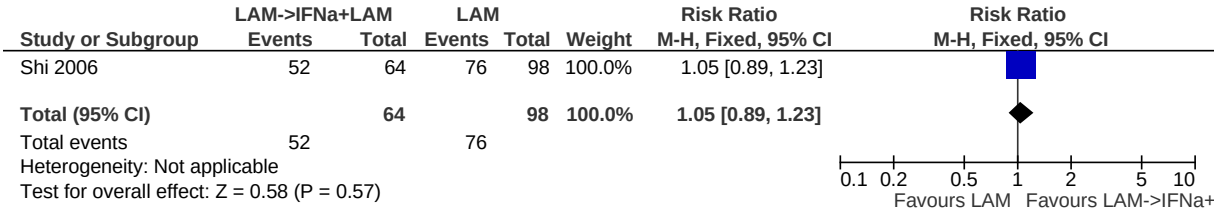
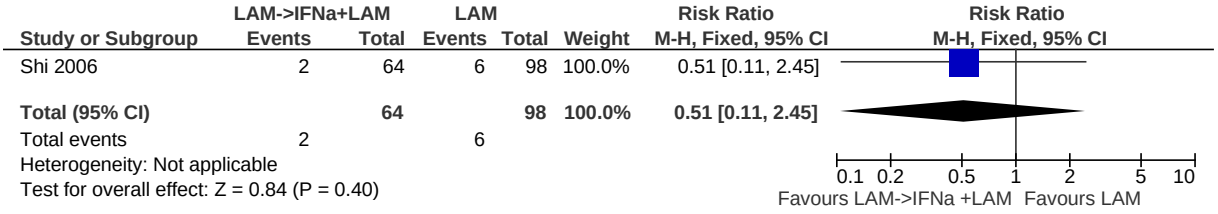


Figure 493: Resistance - lamivudine resistant mutations (end of 24 weeks treatment)



Switching from lamivudine to lamivudine plus interferon alpha-2b combination therapy to interferon alpha-2b alone versus lamivudine for antiviral treatment naïve adults

Figure 494: % of patients with ALT normalization (end of 48 weeks treatment)

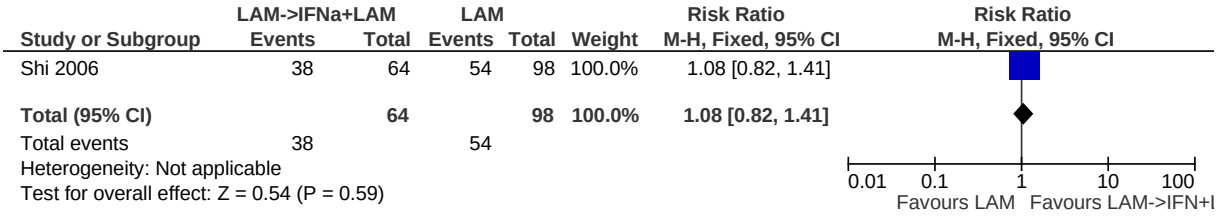


Figure 495: % of patients with undetectable HBV DNA (<1000 copies/ml) (end of 48 weeks treatment)

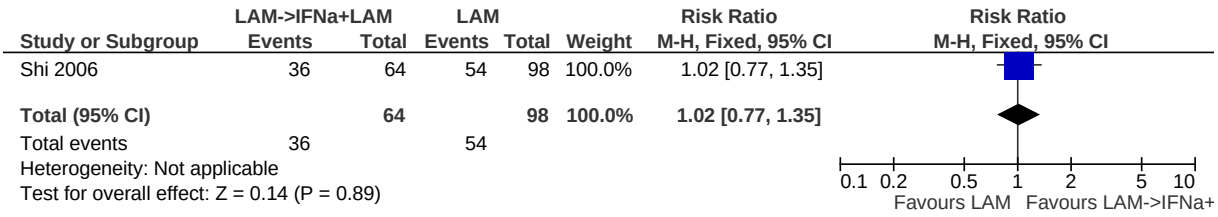


Figure 496: Resistance - lamivudine resistant mutations (end of 48 weeks treatment)

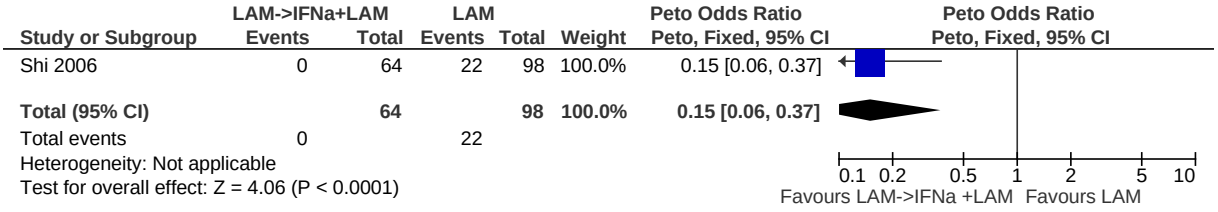


Figure 497: % of patients with ALT normalization (end of 24 weeks follow up)

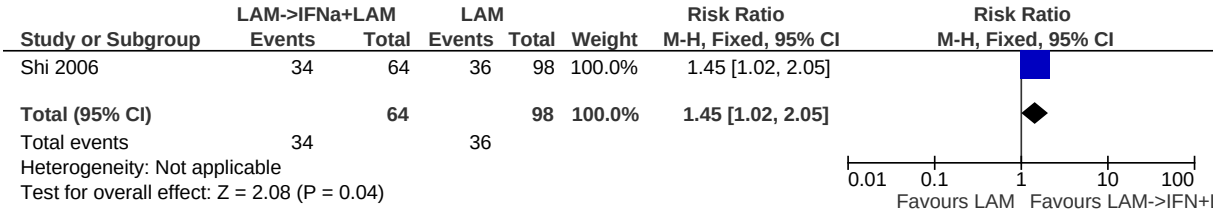
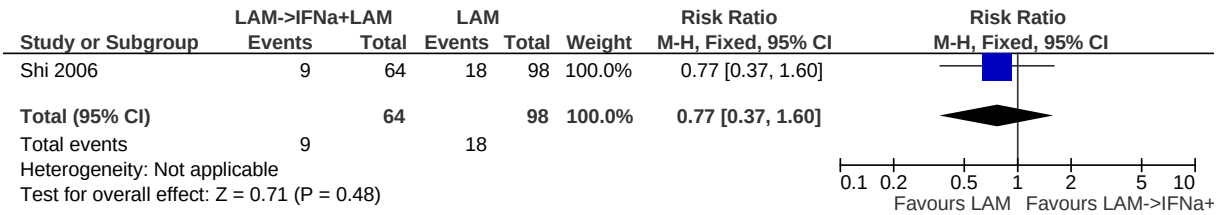


Figure 498: % of patients with undetectable HBV DNA (<1000 copies/ml) (end of 24 weeks follow up)



Switching from lamivudine plus adefovir combination therapy to adefovir monotherapy versus continuing lamivudine plus adefovir combination therapy in lamivudine resistant HBeAg negative adults

Figure 499: **% of patients with undetectable HBV DNA (<3.7 LGE/ml) (12 months after randomisation)**

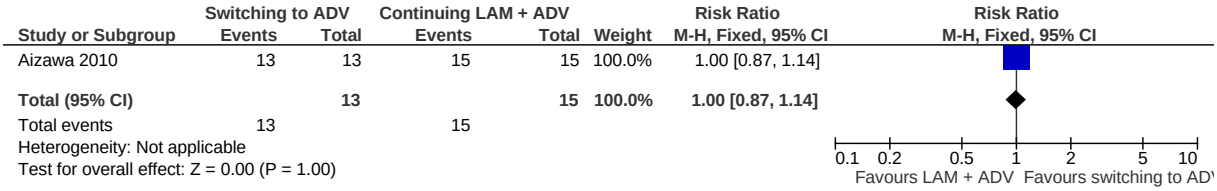


Figure 500: % of patients with ALT normalization (12 months after randomisation)]

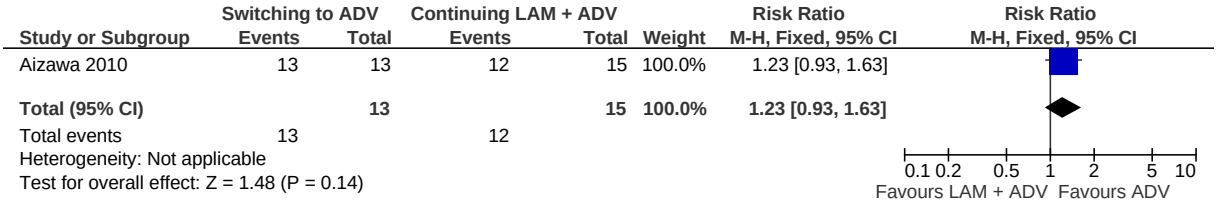


Figure 501: % of patients with HBeAg loss (12 months after randomisation)

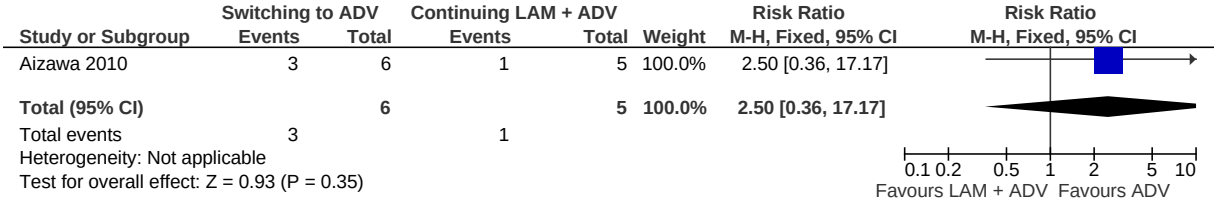


Figure 502: % of patients with HBsAg seroconversion (12 months after randomisation)

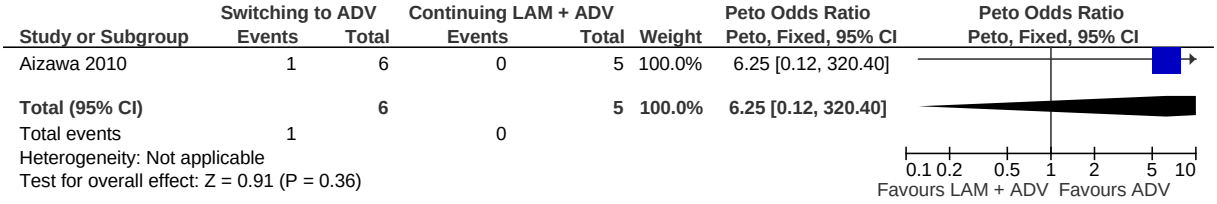


Figure 503: % of patients with undetectable HBV DNA (<3.7 LGE/ml) (24 months after randomisation)

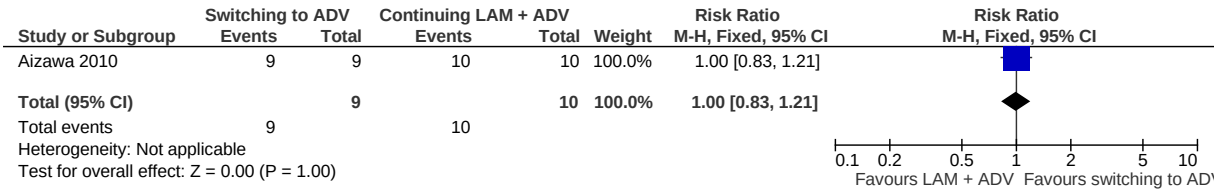


Figure 504: **% of patients with ALT normalization (24 months after randomization)**

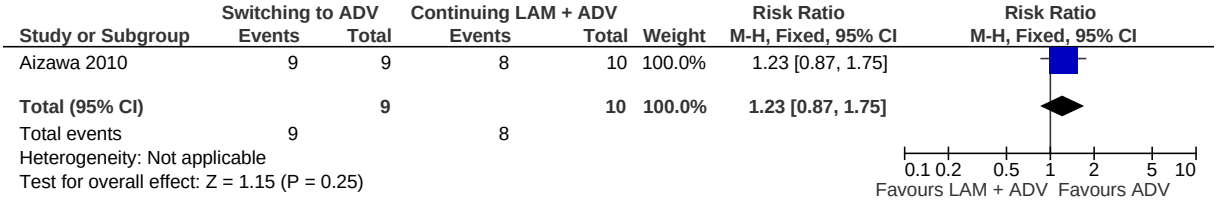


Figure 505: % of patients with HBeAg loss (24 months after randomization)

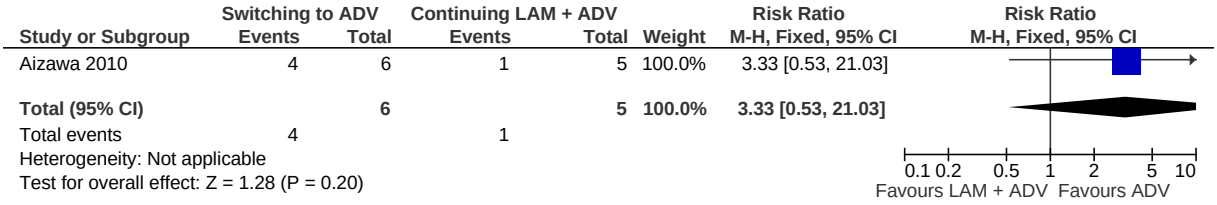


Figure 506: <Insert graphic title here>

% of patients with undetectable HBV DNA (<3.7 LGE/ml) (30 months after randomization)

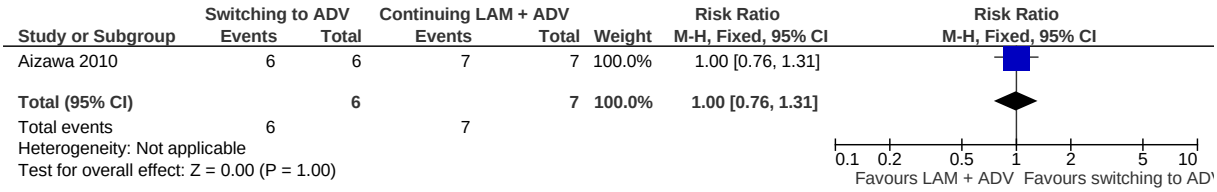


Figure 507: % of patients with ALT normalization (30 months after randomization)

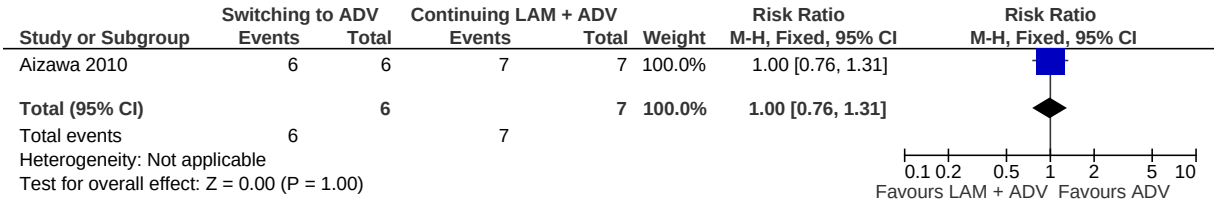
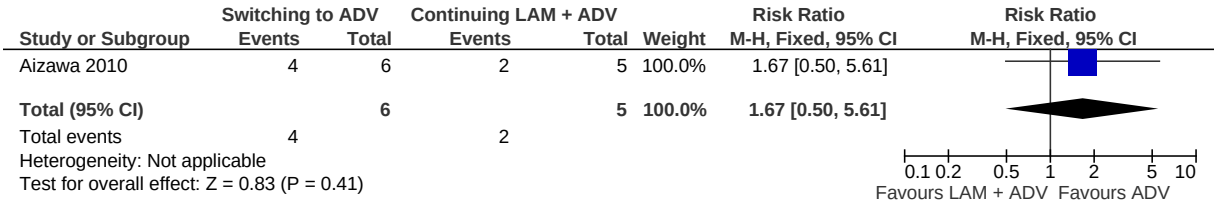


Figure 508: % of patients with HBeAg loss (30 months after randomization)



Switching from lamivudine to adefovir plus lamivudine combination therapy versus switching from lamivudine to adefovir monotherapy in lamivudine resistant HBeAg negative patients

Figure 509: Undetectable HBV DNA <1000 copies/mL.

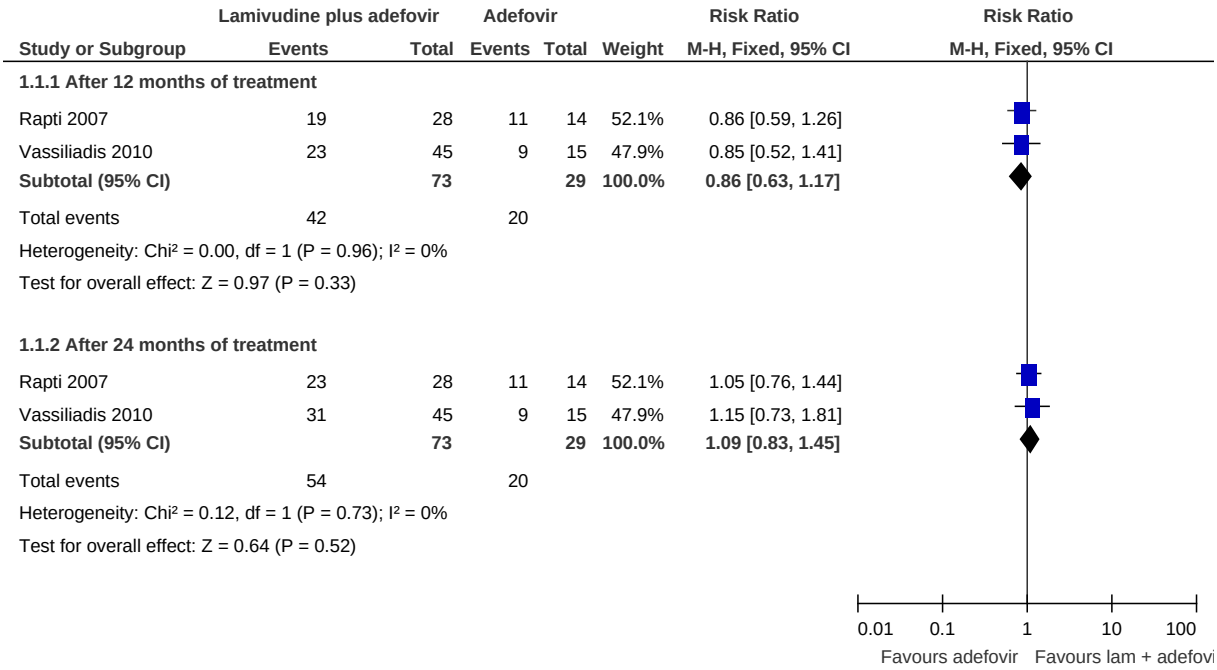
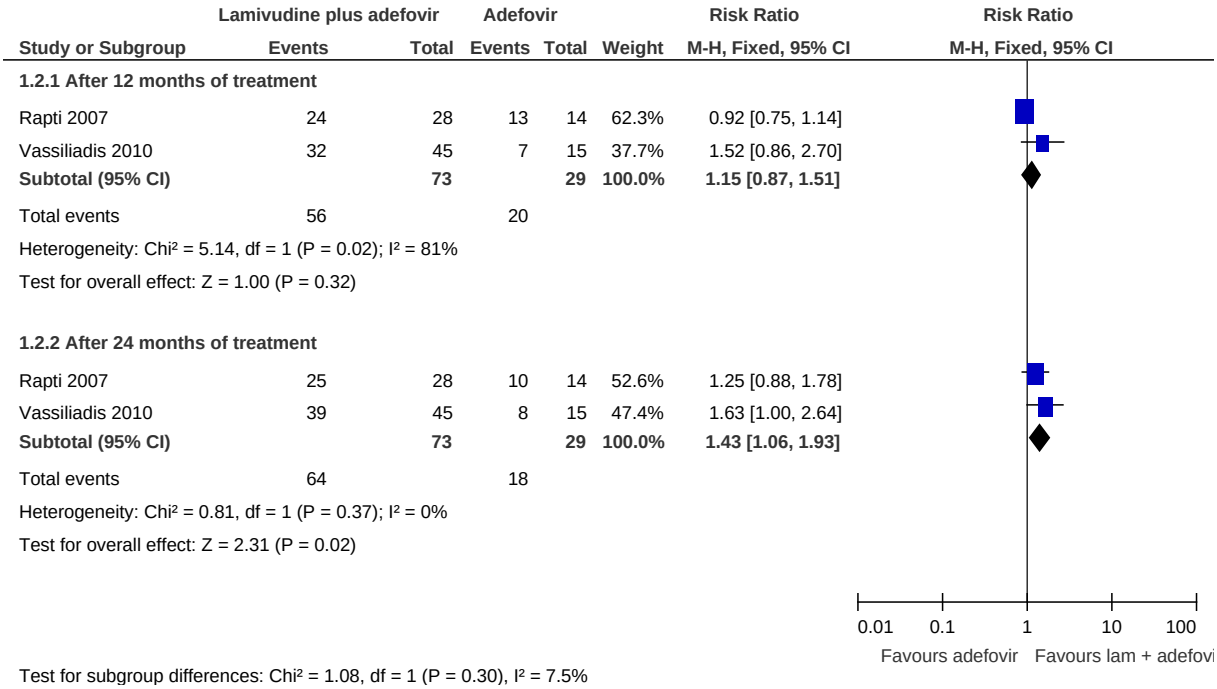


Figure 510: **ALT normalisation.**



Switching from lamivudine to adefovir versus lamivudine plus adefovir combination therapy in lamivudine resistant HBeAg negative patients

Figure 511: % of patients with undetectable HBV DNA (<2000 copies/ml) (assessed at end of 3 months treatment)

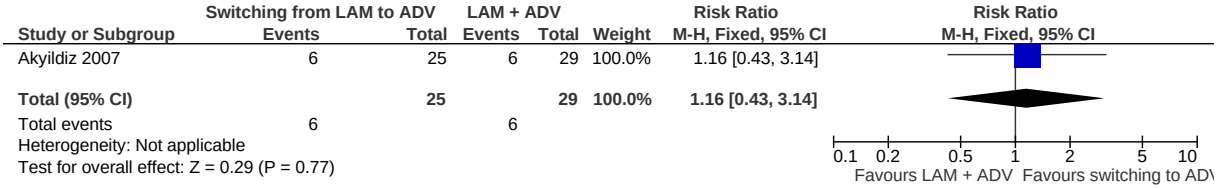


Figure 512: % of patients with undetectable HBV DNA (<2000 copies/ml) (assessed at 3 months follow up)

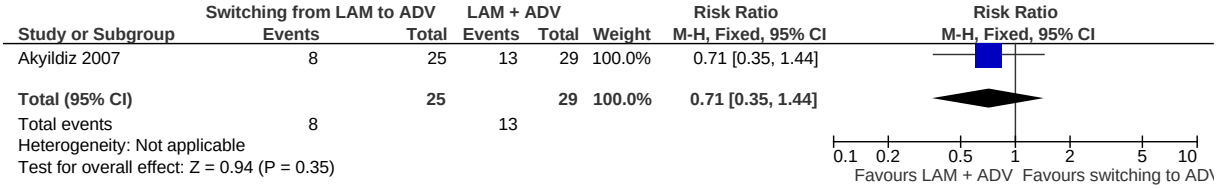


Figure 513: % of patients with undetectable HBV DNA (<2000 copies/ml) (assessed at 9 months follow up)

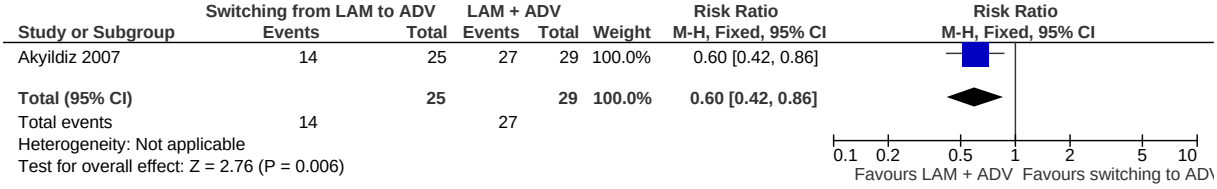


Figure 514: % of patients with ALT normalisation (assessed at end of 3 months treatment)

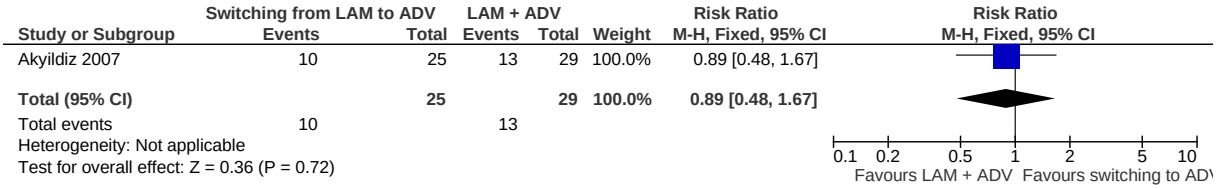


Figure 515: % of patients with ALT normalization (assessed at 3 months follow up)

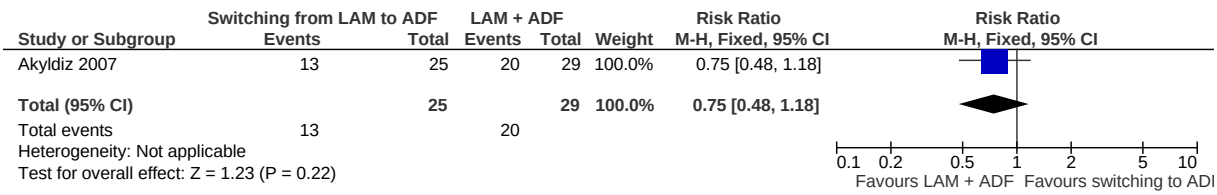
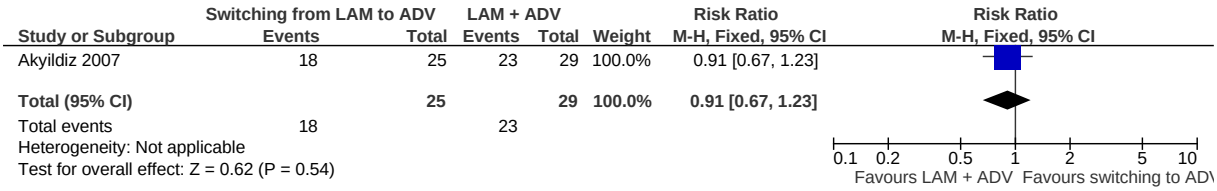


Figure 516: % of patients with ALT normalization (assessed at 9 months follow up)



Switching from lamivudine to entecavir versus continuing lamivudine in HBeAg negative patients who responded to previous lamivudine treatment

Figure 517: % of patients with undetectable HBV DNA (<2.6 log copies/mL) (mean 24 months treatment).

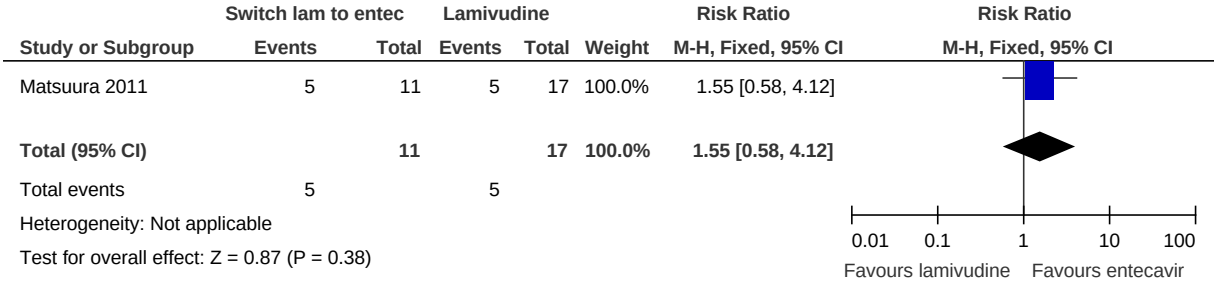
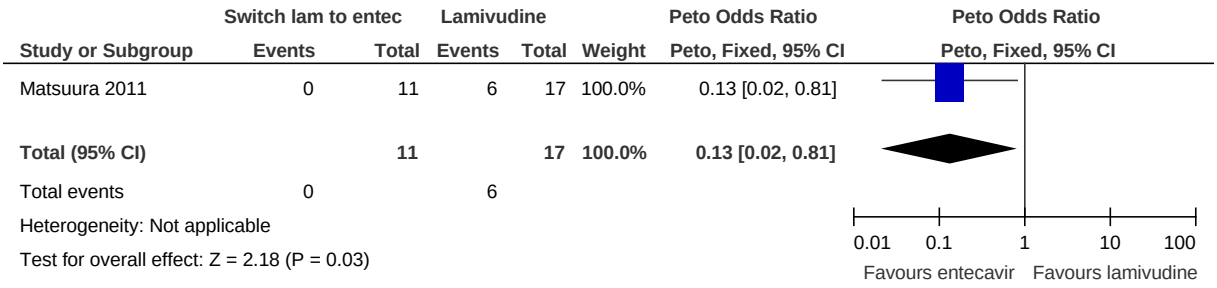


Figure 518: <Insert graphic title here>

Incidence of resistance (mean 24 months treatment).



Switching from entecavir to lamivudine versus continuing entecavir in HBeAg negative patients previously treated with entecavir and undetectable HBV DNA

Figure 519: % of patients with undetectable HBV DNA (<100 copies/ml) (assessed at the end of 96 weeks treatment)

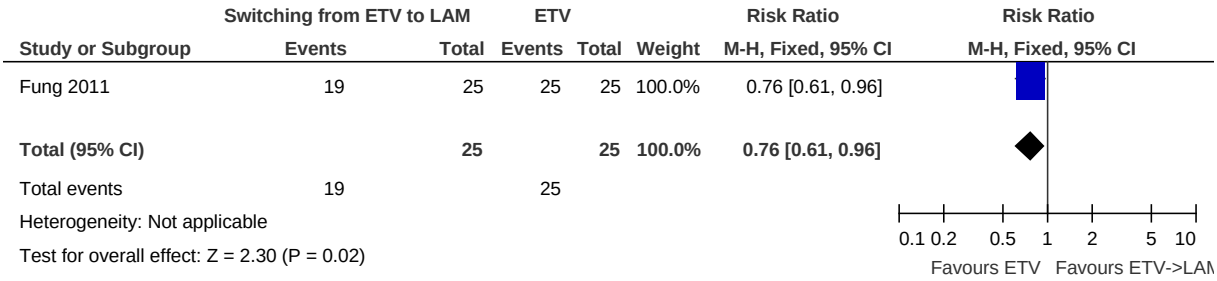


Figure 520: % of patients with ALT normalization (assessed at the end of 96 weeks treatment)

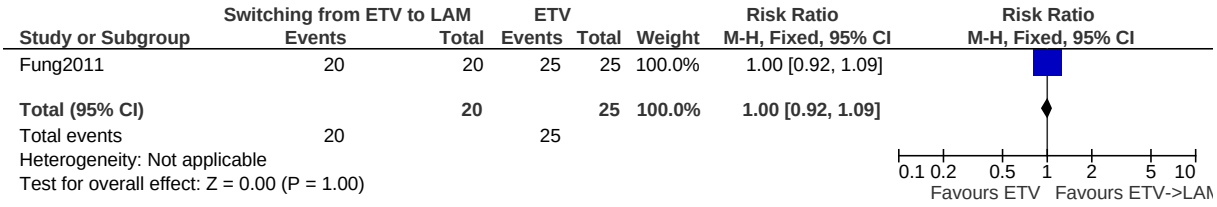
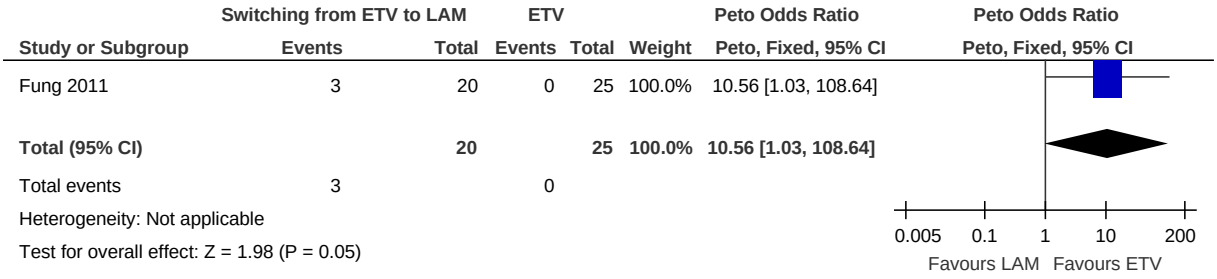
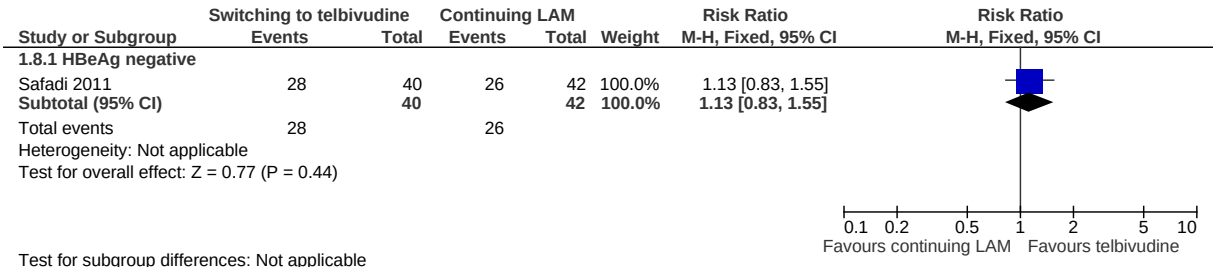


Figure 521: Incidence of resistance (YMDD mutation) (assessed at the end of 96 weeks treatment)



Switching from lamivudine to telbivudine versus continuing lamivudine in patients previously treated with lamivudine and had persistent viraemia

Figure 522: <Insert graphic title here>



G.3.2.3 Sequential antiviral therapy for children with CHB

Interferon alpha versus sequential therapy: lamivudine (2 months) followed by interferon plus lamivudine combination therapy (6 months) followed by lamivudine (4 months)

Figure 523: HBeAg loss (assessed at end of treatment)

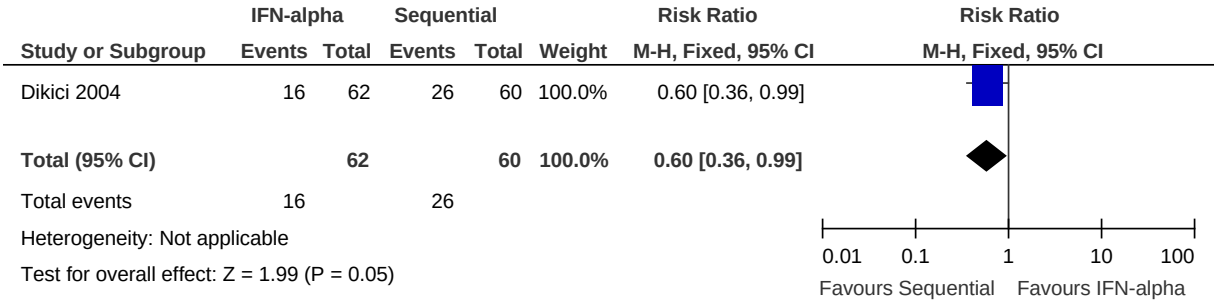


Figure 524: HBeAg seroconversion (assessed at end of treatment)

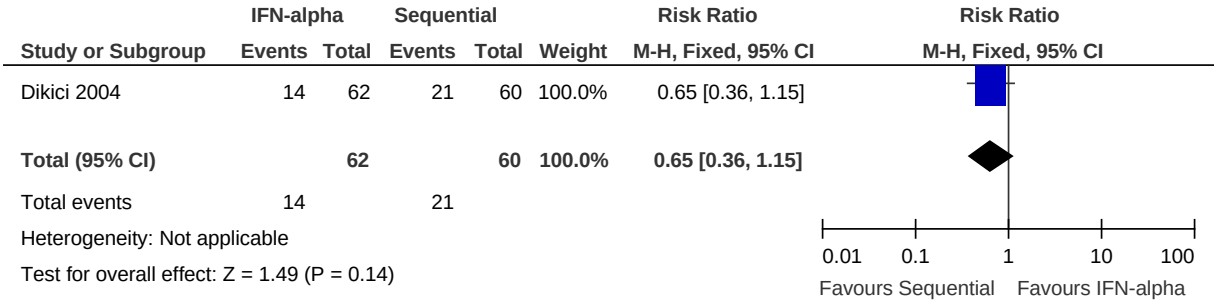


Figure 525: Undetectable DNA (undefined threshold) (assessed at end of treatment)

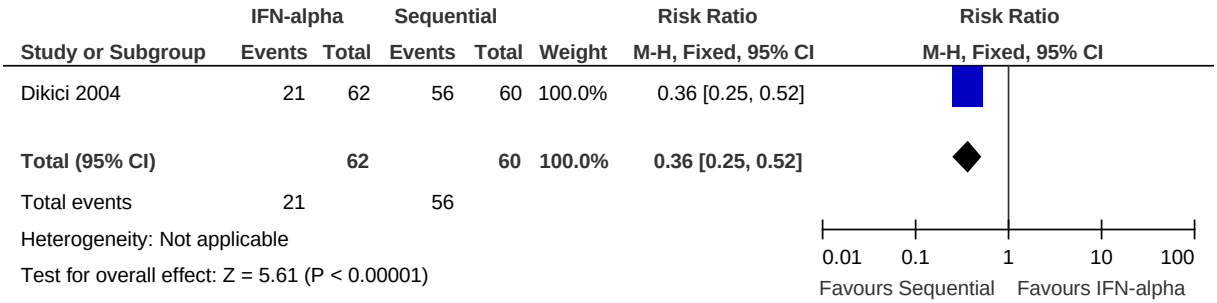


Figure 526: HBsAg seroconversion (assessed at end of treatment)

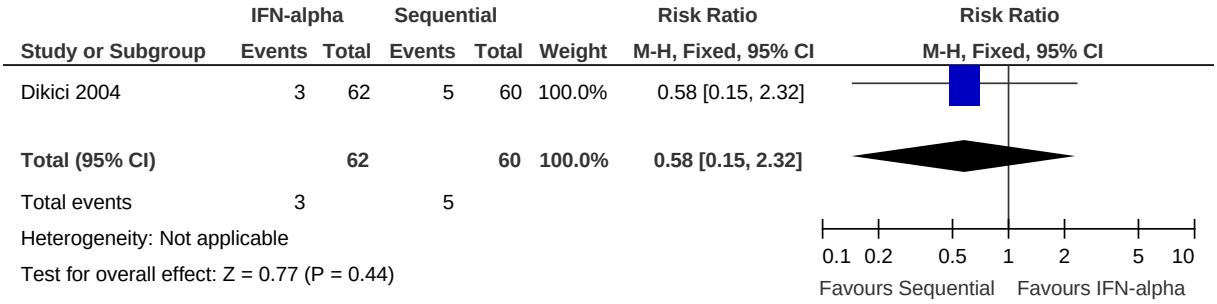


Figure 527: HBeAg loss (assessed at 6 months follow-up)

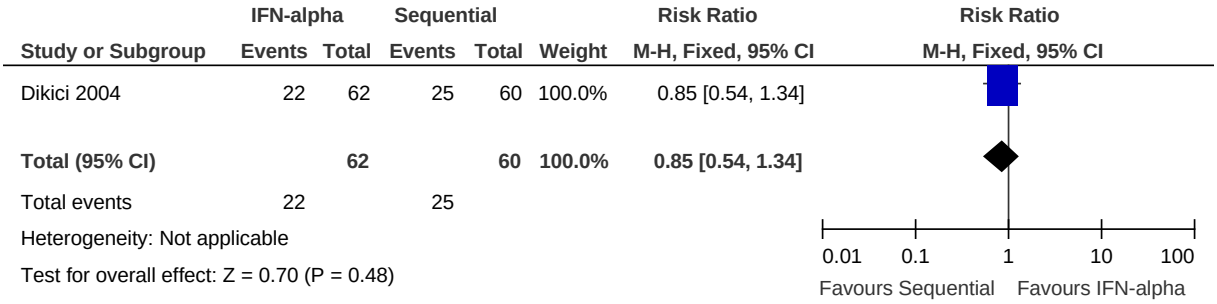


Figure 528: HBeAg seroconversion (assessed at 6 months follow-up)

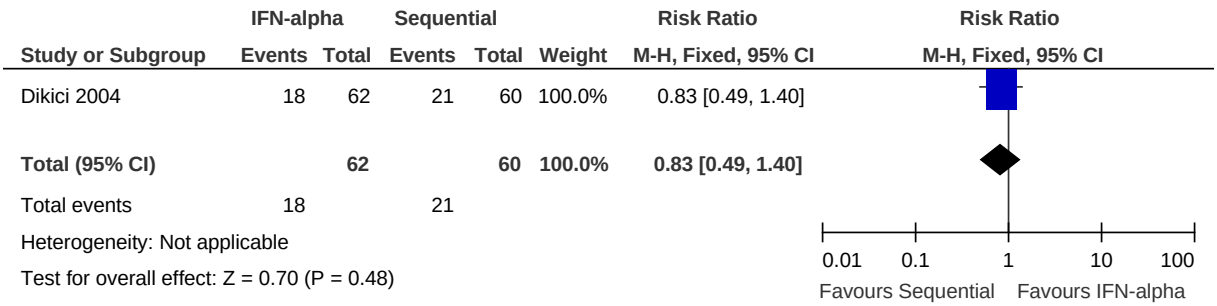


Figure 529: Undetectable DNA (undefined threshold) (assessed at 6 months follow-up)

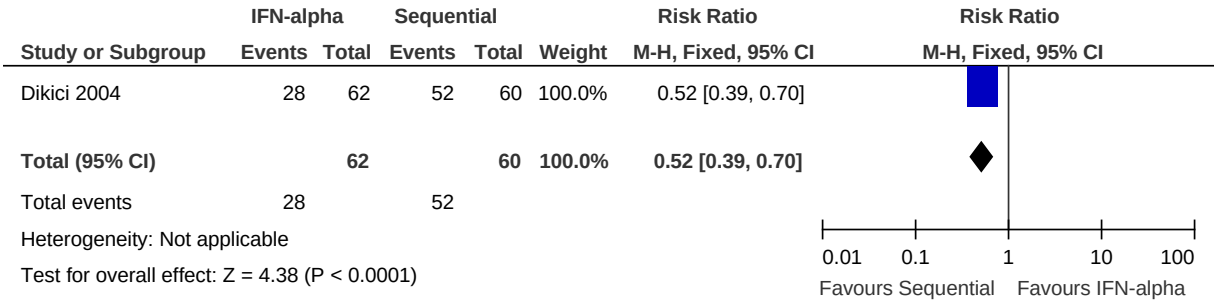


Figure 530: HBeAg loss (assessed at 12 months follow-up)

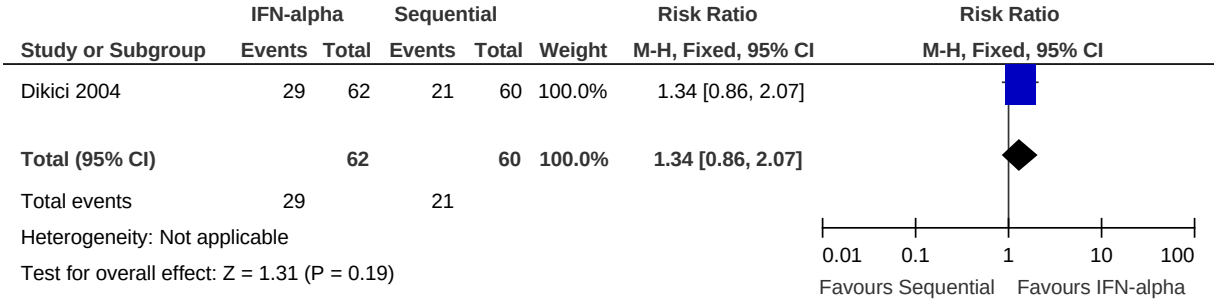


Figure 531: HBeAg seroconversion (assessed at 12 months follow-up)

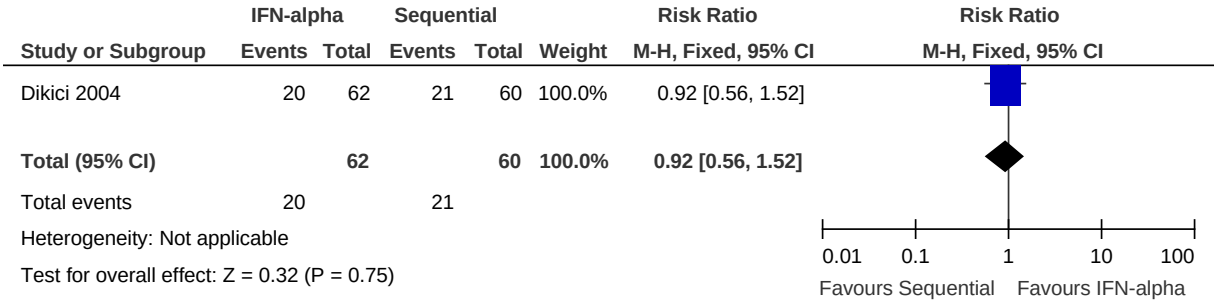


Figure 532: Undetectable DNA (undefined threshold) (assessed at 12 months follow-up)

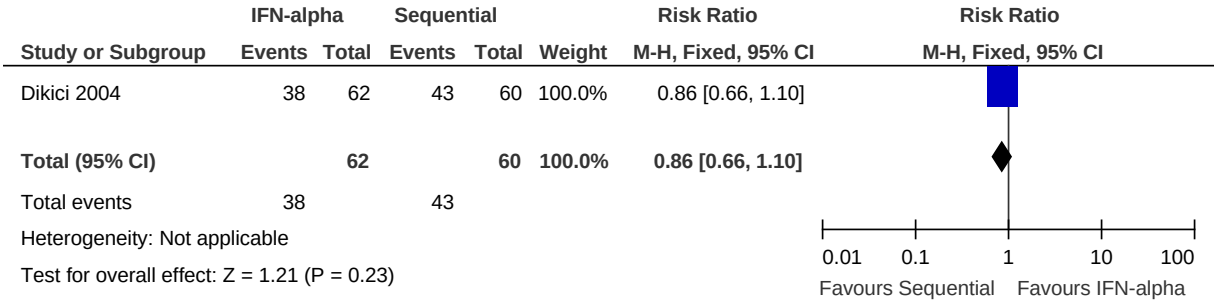
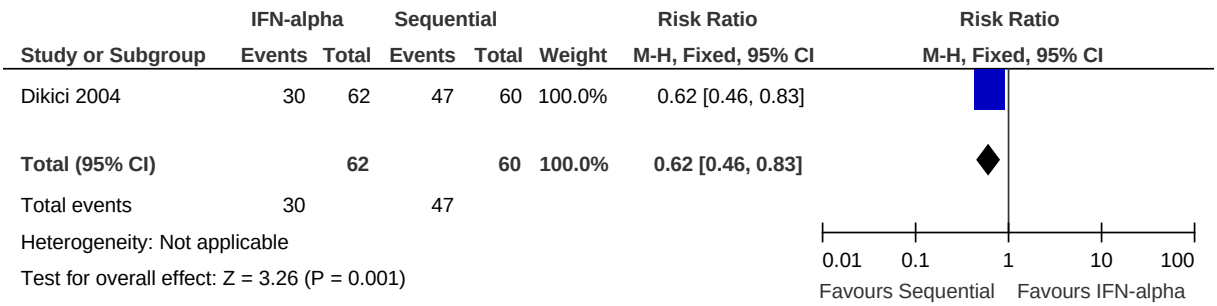


Figure 533: Normalisation of ALT (assessed at 12 months follow-up)



IFN-α + lamivudine (6 months) followed by LAM alone (6-12 months) ("Group 1") vs. Lamivudine (2 months), IFN+ lamivudine (6 months), lamivudine alone (4 months) ("Group 2")

Figure 534: HBeAg loss (assessed at 12 months)

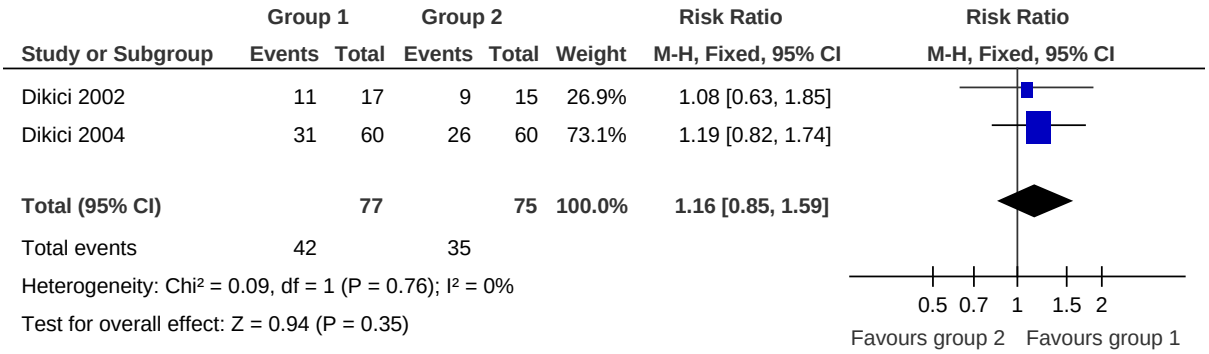


Figure 535: HBeAg seroconversion (assessed at 12 months)

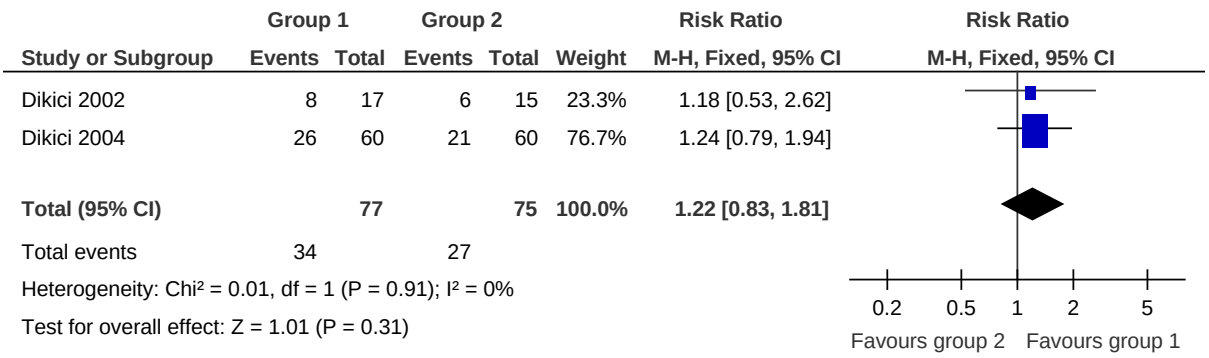


Figure 536: Clearance of HBsAg (assessed at 12 months)

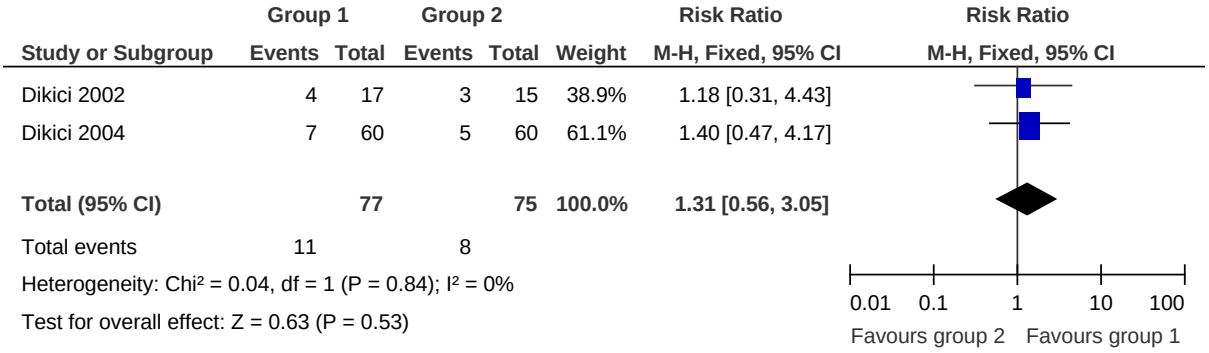


Figure 537: HBsAg seroconversion (assessed at 12 months)

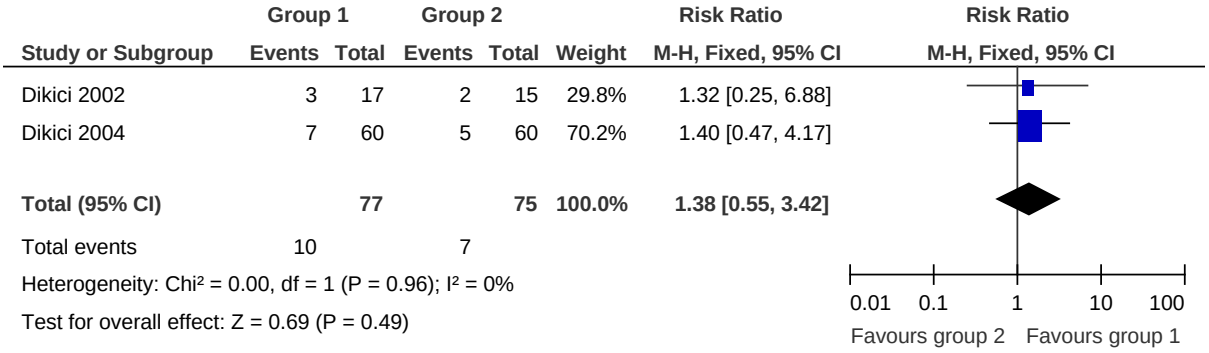


Figure 538: Undetectable HBV DNA (assessed at 12 months).

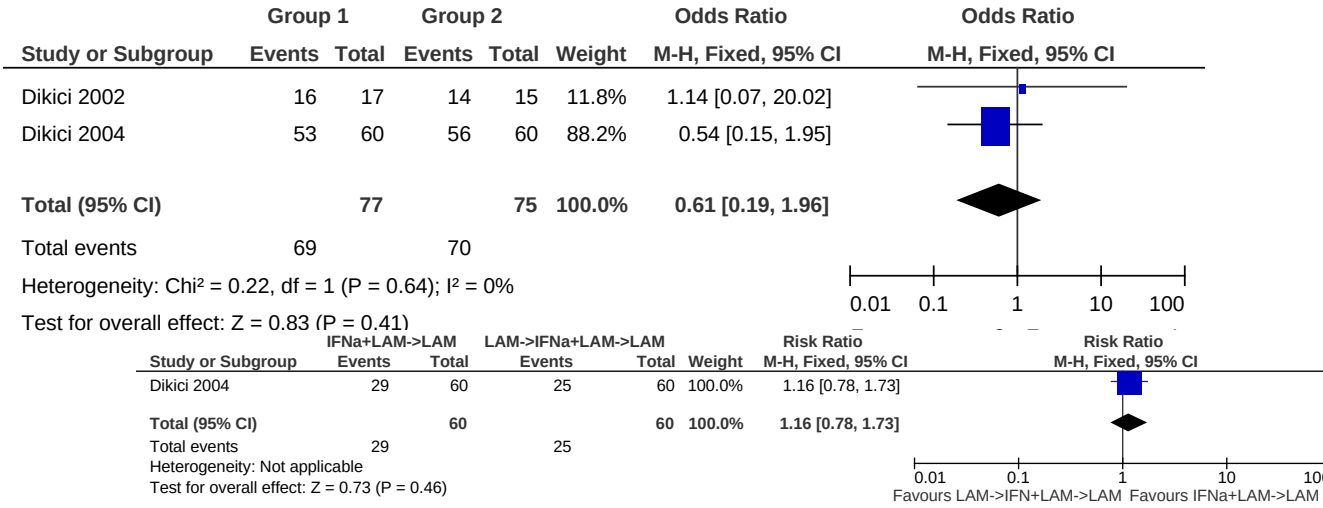


Figure 539: ALT normalisation (assessed at 12 months).

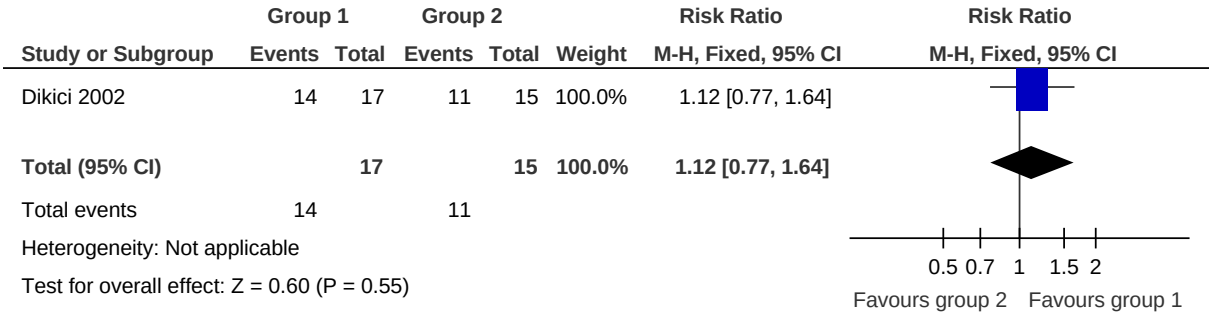


Figure 540: Clearance of HBeAg (18 months)

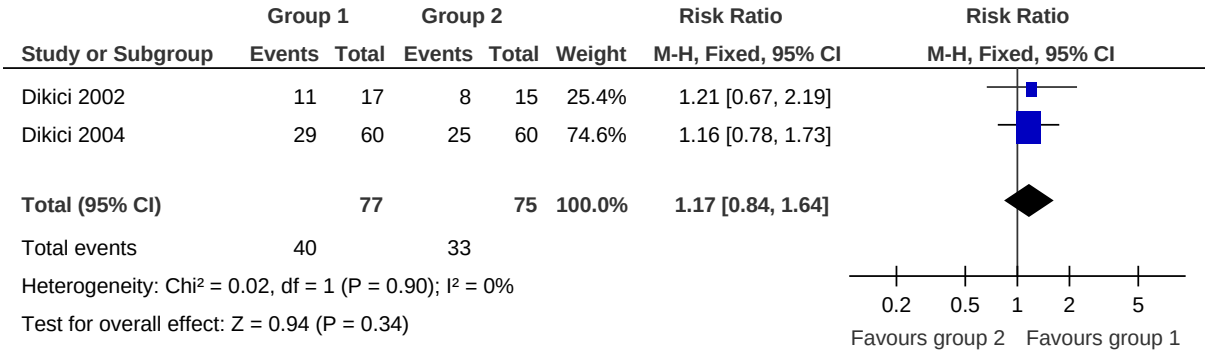


Figure 541: Seroconversion to anti-HBe (18 months).

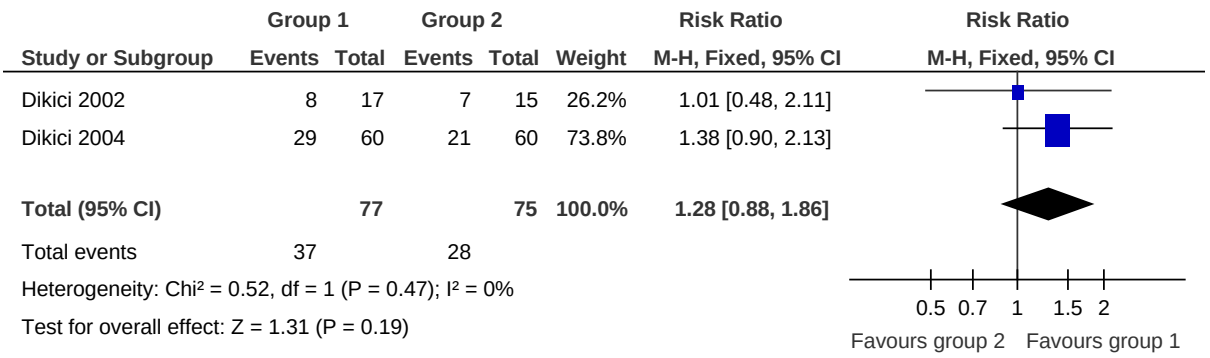


Figure 542: Clearance of HBsAg (18 months).

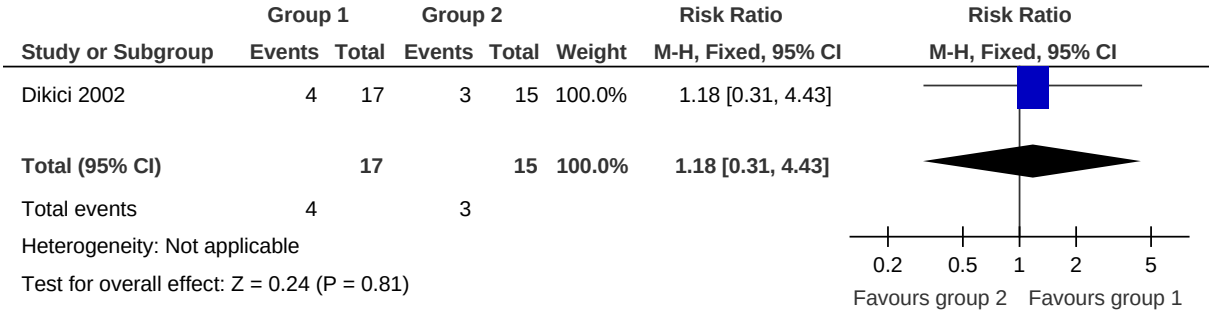


Figure 543: Seroconversion to anti-HBs (18 months).

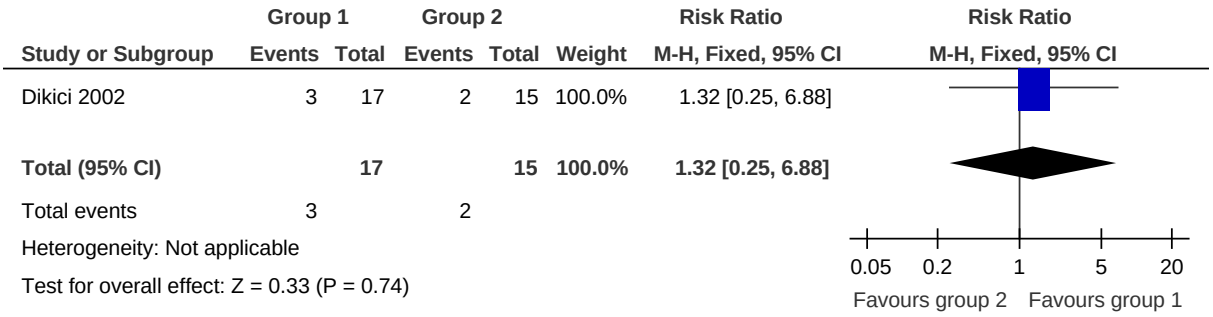


Figure 544: Undetectable HBV DNA (18 months).

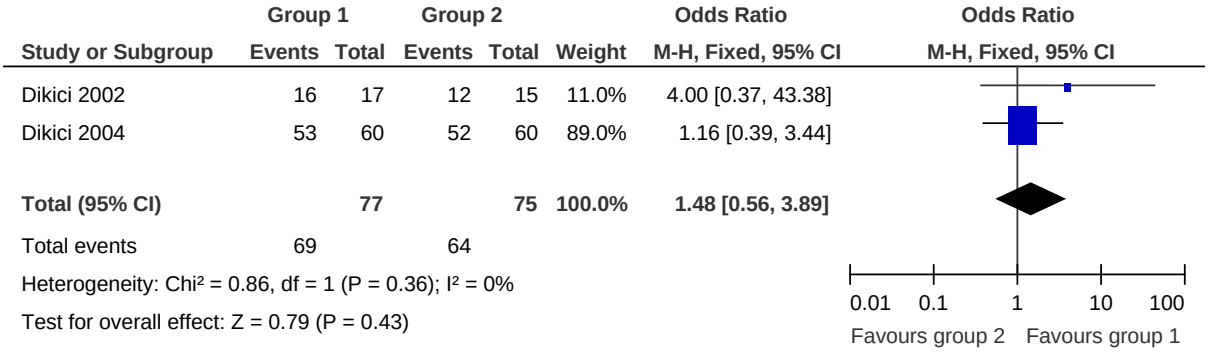


Figure 545: **ALT normalisation (18 months).**

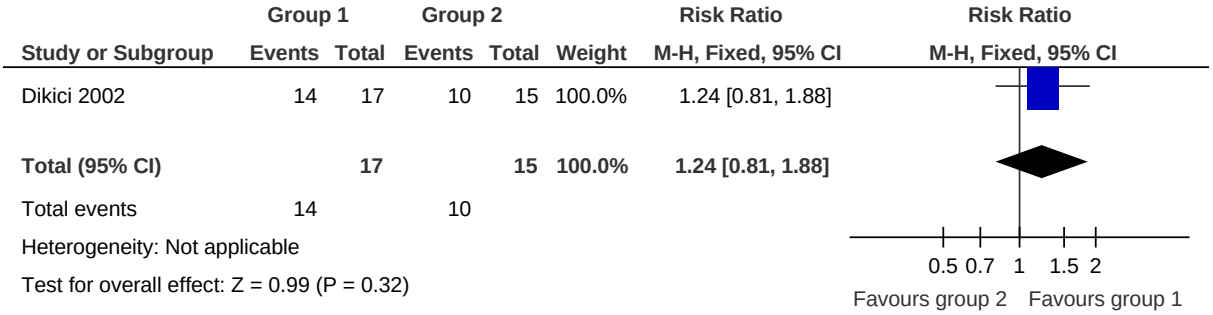


Figure 546: Clearance of HBeAg (24 months

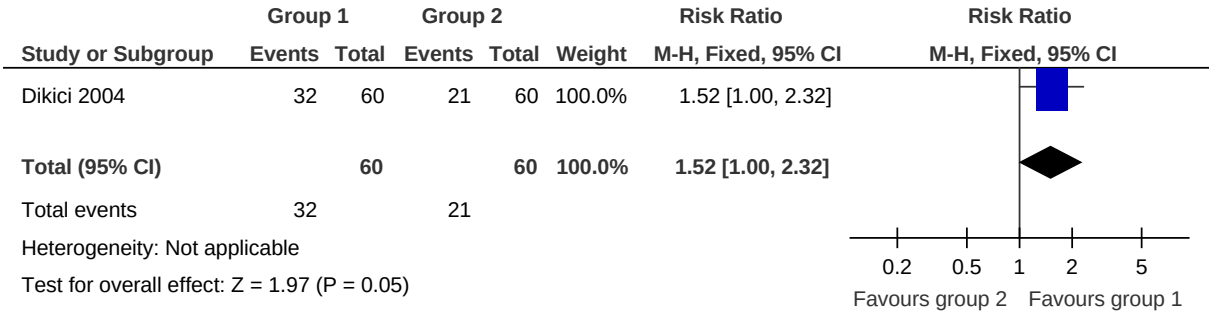


Figure 547: **Seroconversion to anti-HBe (24 months).**

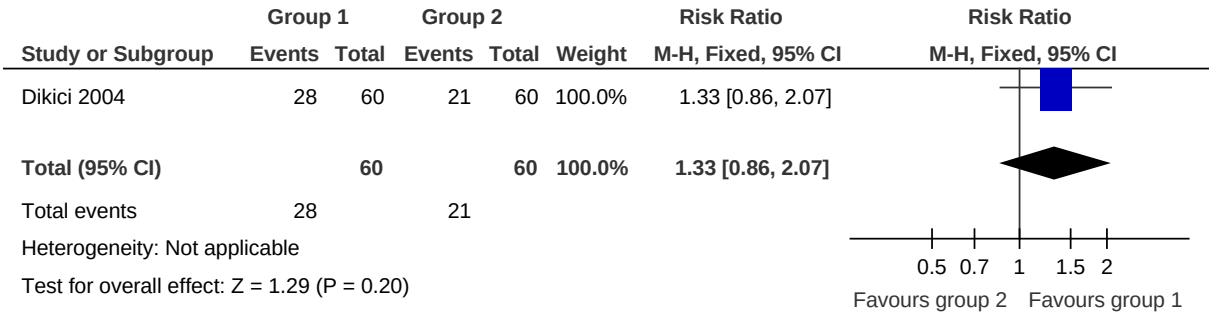


Figure 548: **Undetectable HBV DNA (24 months).**

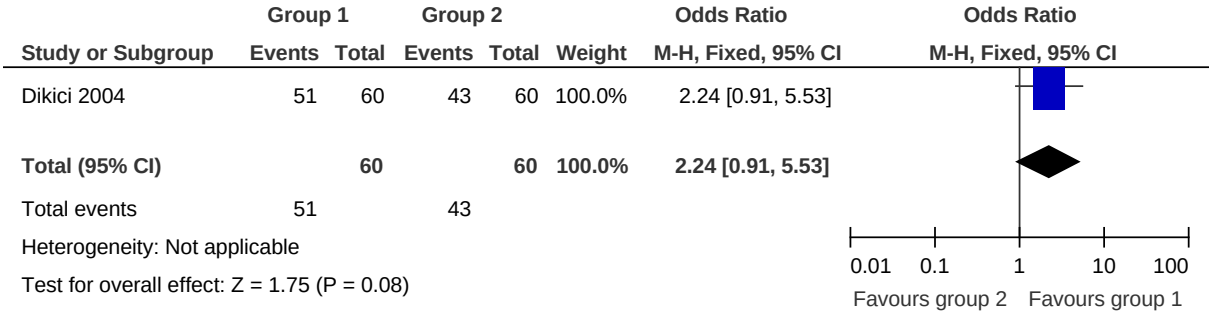
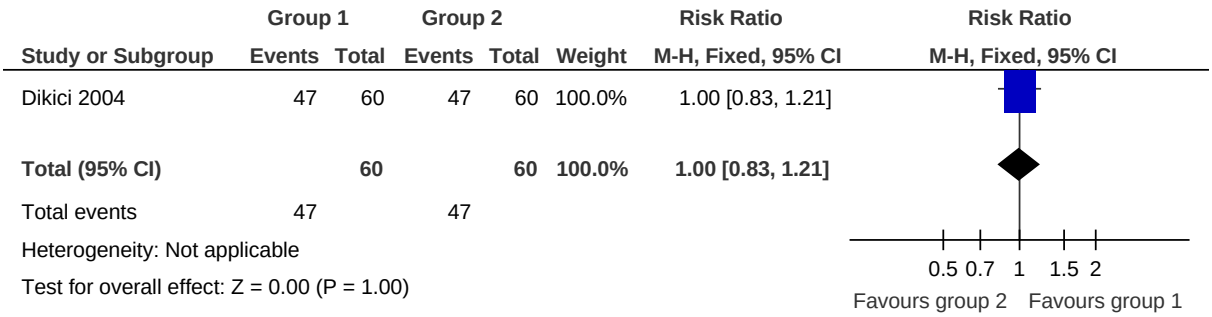


Figure 549: **ALT normalisation (24 months).**



IFN-α + lamivudine (6 months) followed by LAM alone (6 months) vs. IFN-α alone (6 months)

Figure 550:**HBeAg clearance (end of treatment).**

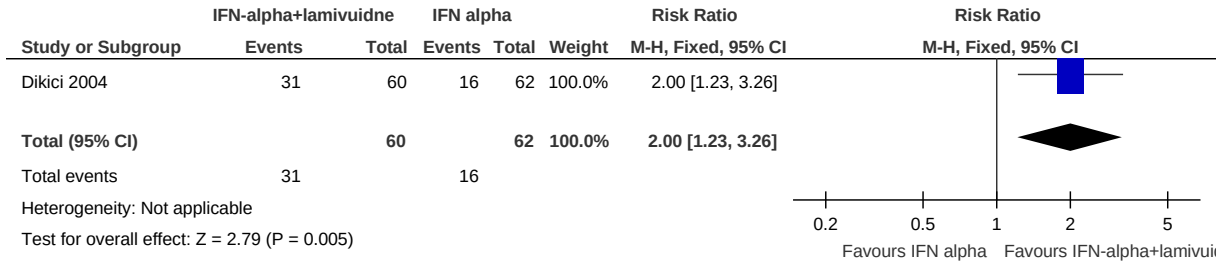


Figure 551: **Anti-HBe seroconversion (end of treatment).**

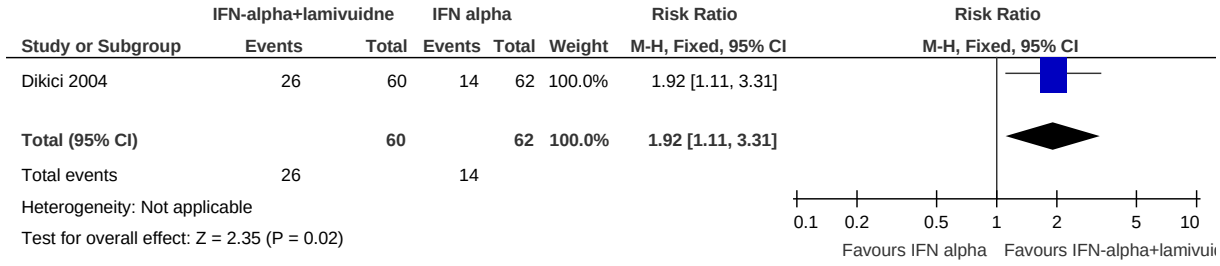


Figure 552: **Undetectable DNA (end of treatment).**

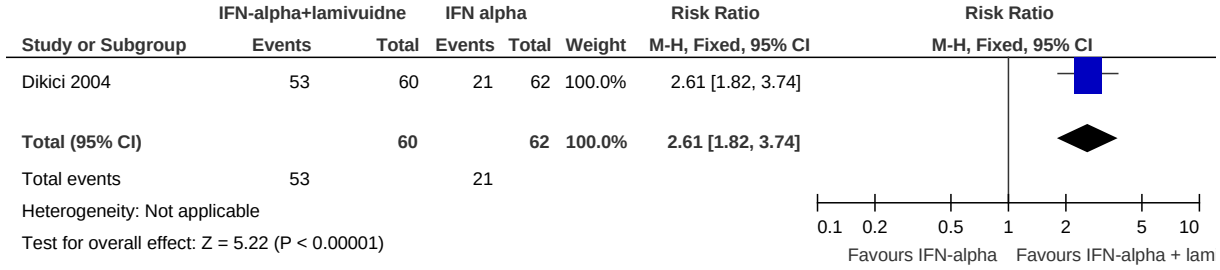


Figure 553: **HBsAg seroconversion (end of treatment).**

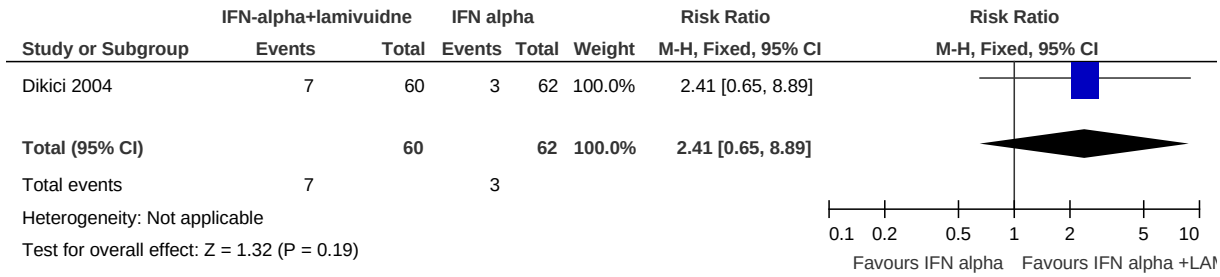


Figure 554: **HBeAg clearance (6 months follow-up).**

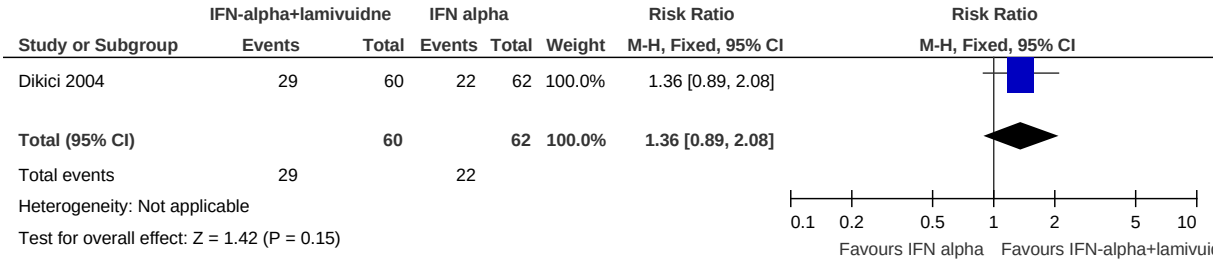


Figure 555: **Anti-HBe seroconversion (6 months follow-up).**

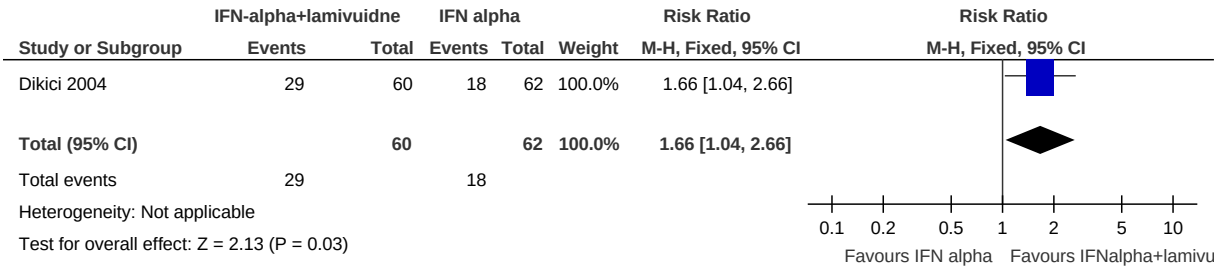


Figure 556: **Undetectable DNA (6 months follow-up).**

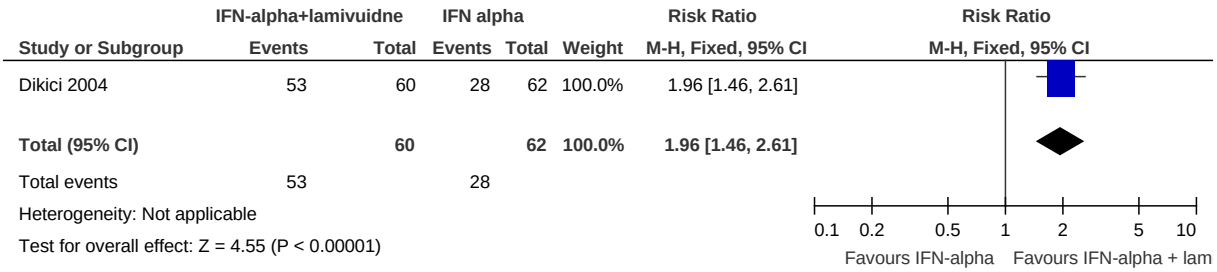


Figure 557: **HBeAg clearance (12 months follow-up).**

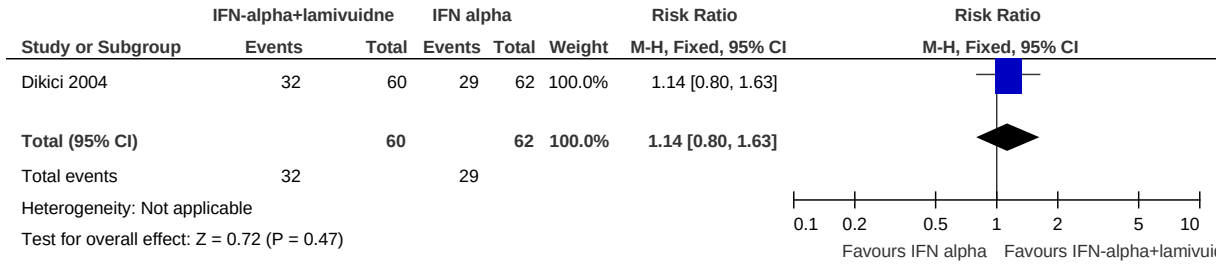


Figure 558: **Anti-HBe seroconversion (12 months follow-up).**

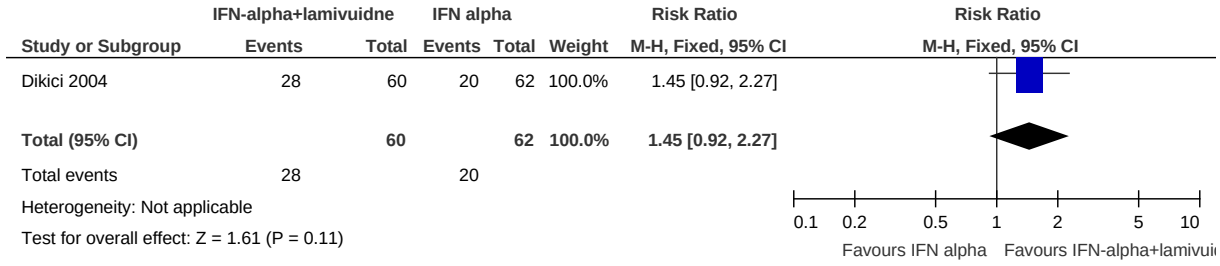


Figure 559: **Undetectable DNA (12 months follow-up).**

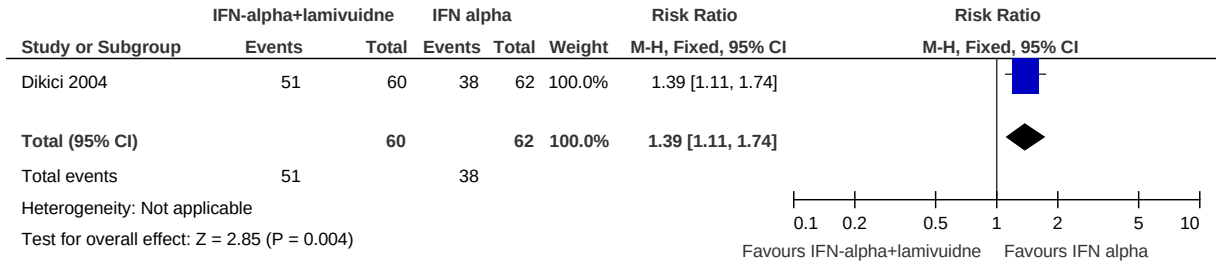
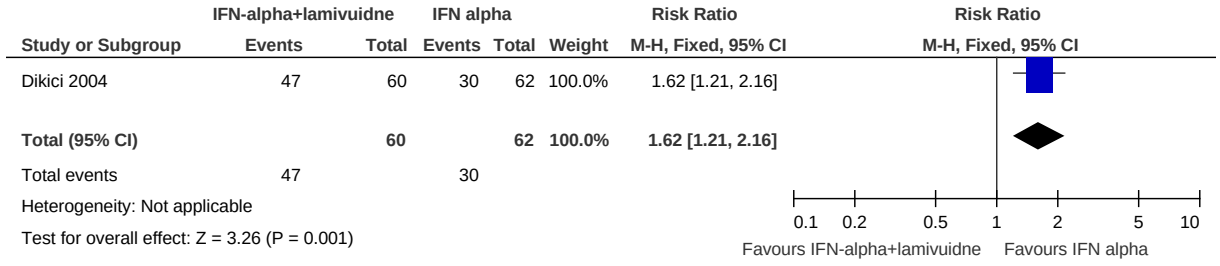


Figure 560: **Normalisation of ALT (12 months follow-up).**



Simultaneous LAM + IFN alpha 2a (6 months) vs. sequential LAM alone 2 months then add IFN alpha 2a (6 months)

Figure 561: **ALT normalization (12 months).**

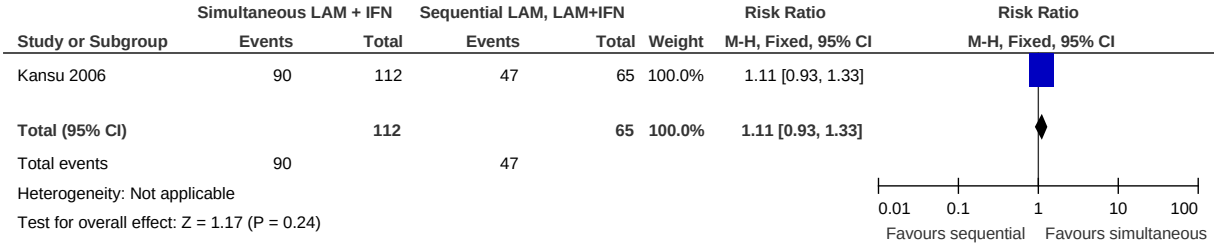


Figure 562: Anti HBe seroconversion (12 months)

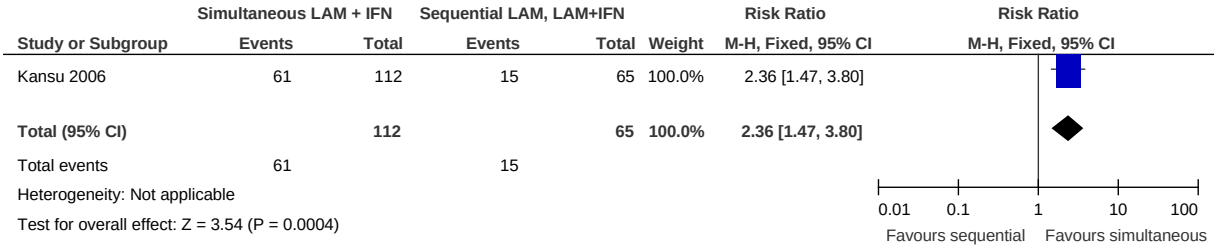


Figure 563: **Undetectable HBV DNA (<5pg/mL) (12 months).**

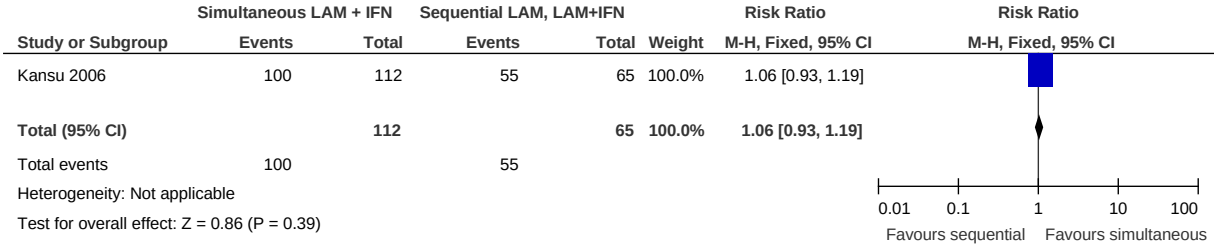


Figure 564: **Breakthrough HBV DNA (12 months).**

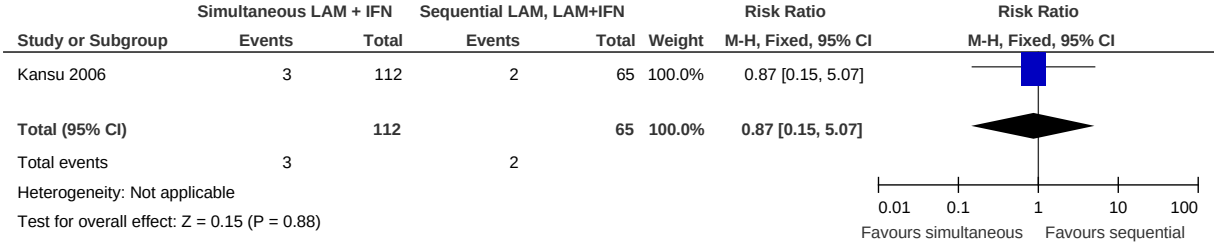


Figure 565: **ALT normalization (18 months).**

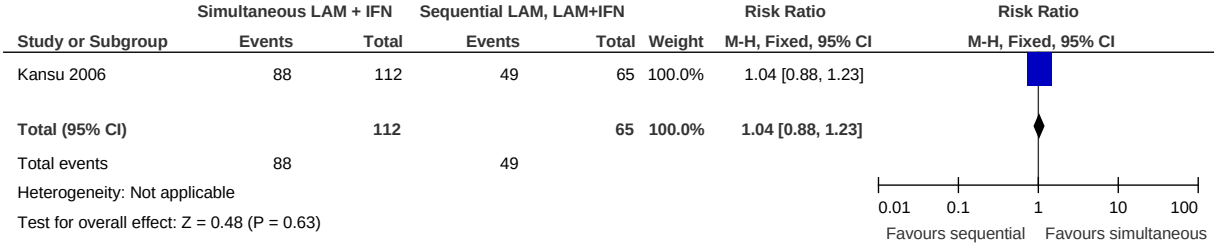


Figure 566: **Anti HBe seroconversion (18 months).**

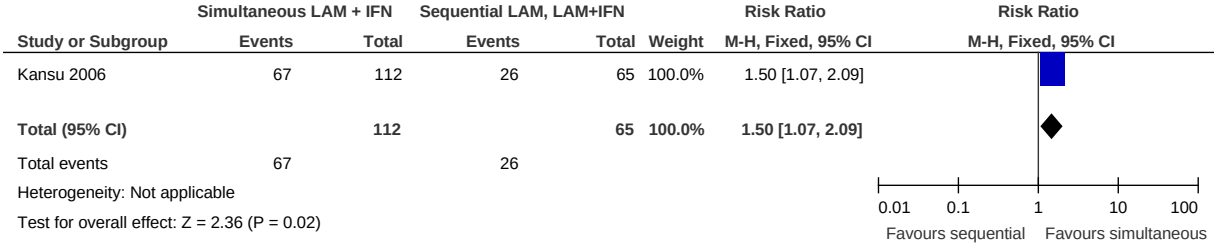


Figure 567: Undetectable HBV DNA (<5pg/mL) (18 months

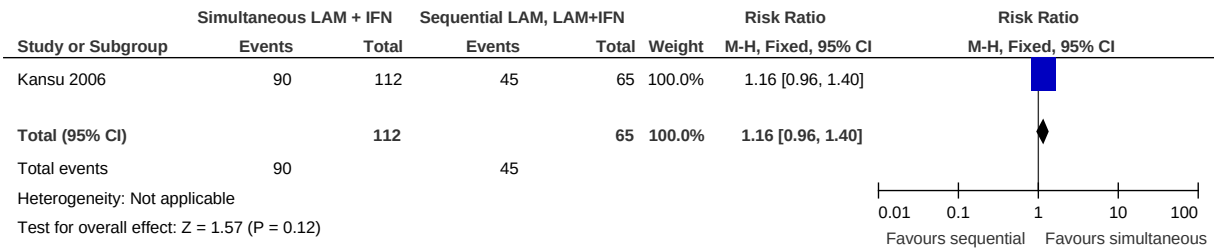


Figure 568: **Breakthrough HBV DNA (18 months).**

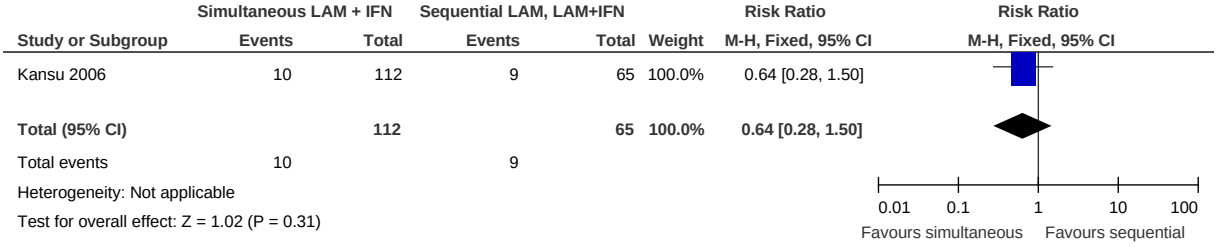


Figure 569: **ALT normalization (24 months).**

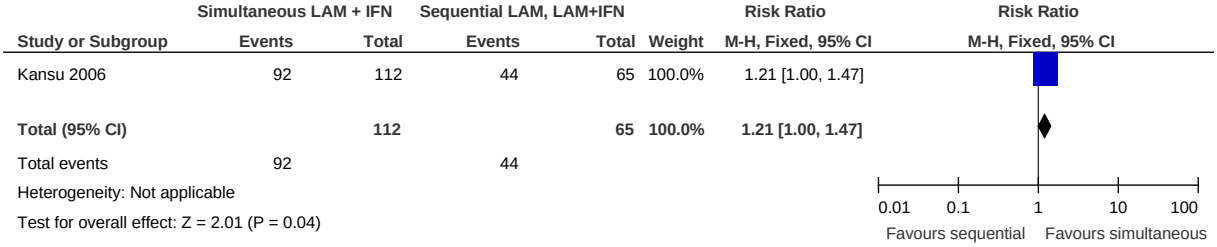


Figure 570: **Anti HBe seroconversion (24 months).**

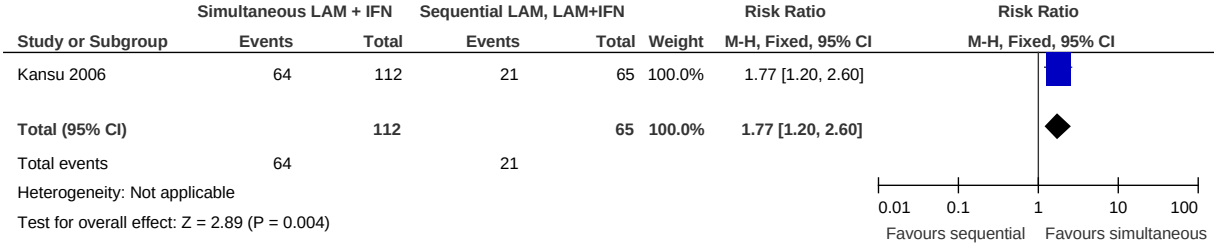


Figure 571: **Undetectable HBV DNA (<5pg/mL) (24 months).**

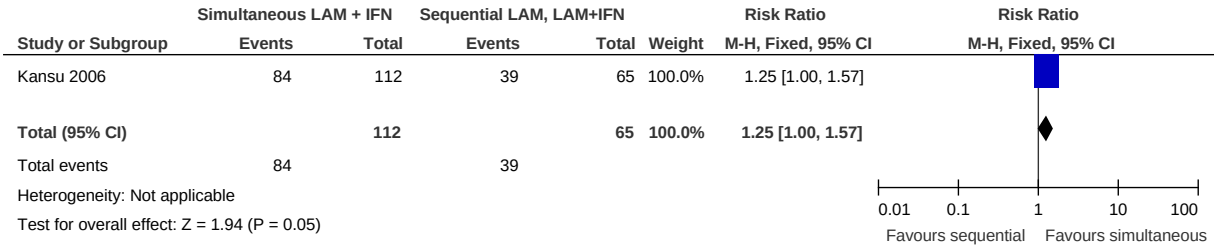


Figure 572: **Breakthrough HBV DNA (24 months).**

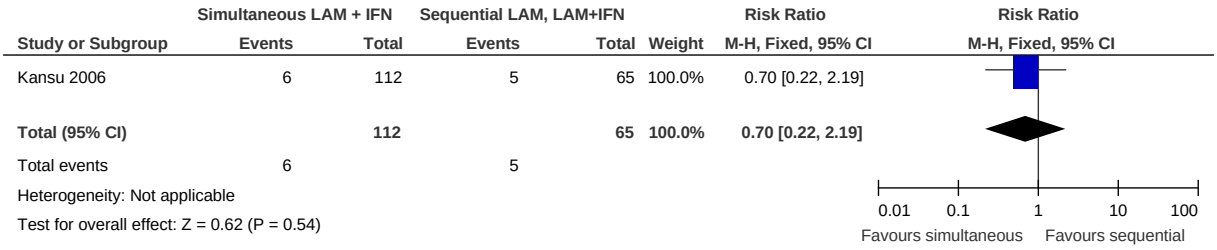
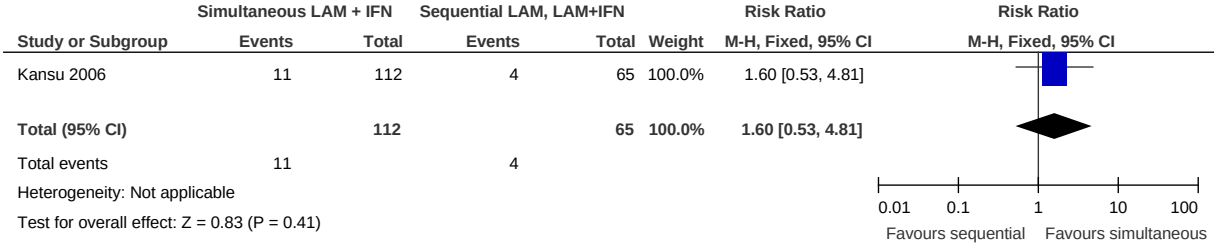


Figure 573: **Anti HBs seroconversion (24 months).**



G.3.3 Cirrhosis and liver decompensation

G.3.3.1 Compensated cirrhosis (or advanced fibrosis) - HBeAg positive

Entecavir versus lamivudine (advanced fibrosis/cirrhosis)

Figure 574: % of patients with undetectable HBV DNA (<300copies/mL) (assessed at end of 48 weeks treatment)

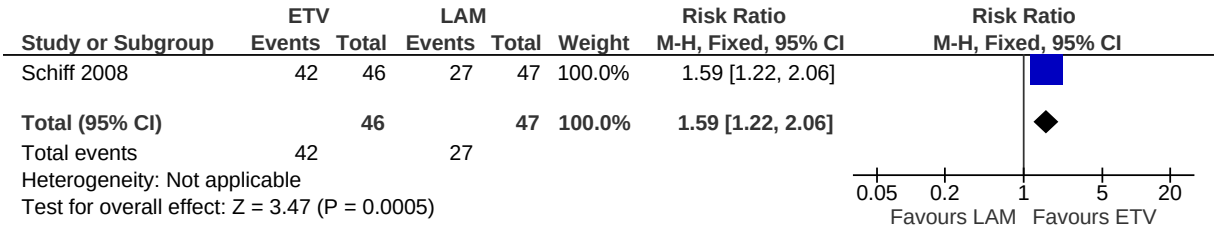
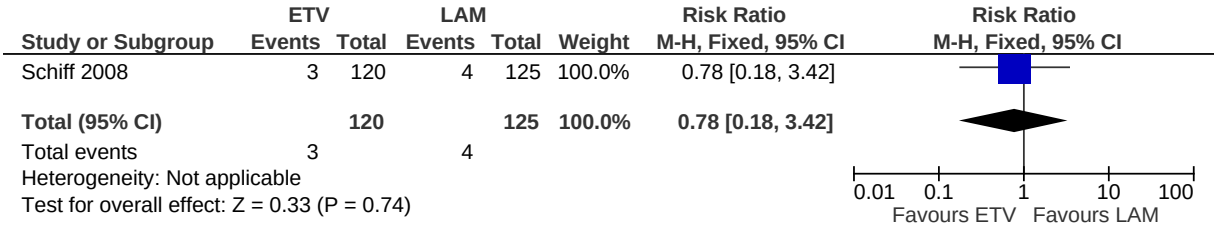


Figure 575: Mortality (3 groups combined: HBeAg positive, negative and lamivudine refractory)



Lamivudine versus placebo (advanced fibrosis/cirrhosis)

Figure 576: % of patients with incidence of hepatocellular carcinoma (assessed at end of 48 weeks treatment)

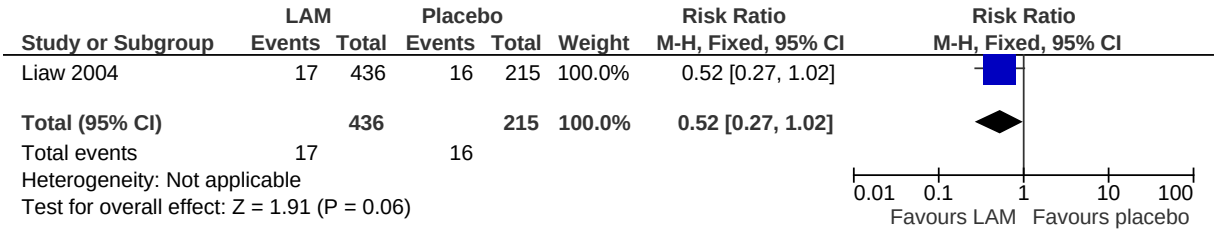


Figure 577: Mortality (assessed at end of 48 weeks treatment)

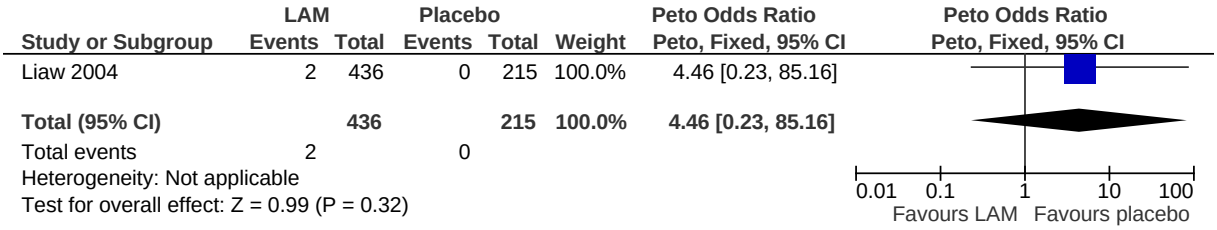


Figure 578: % of patients with incidence of resistance (assessed at end of 48 weeks treatment)

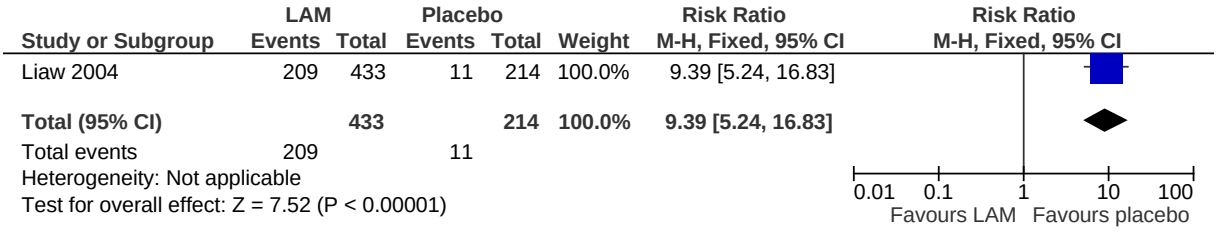
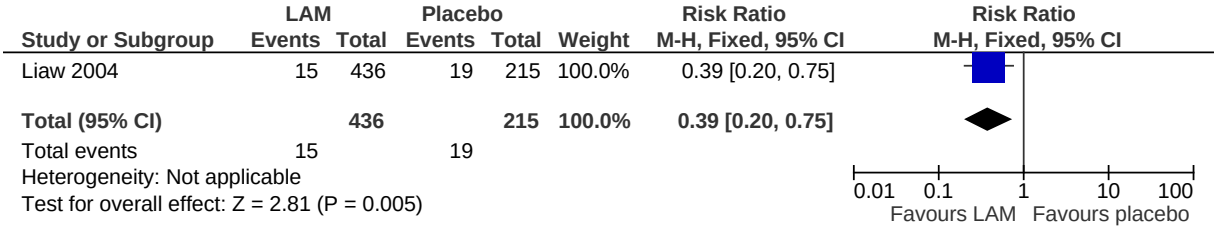


Figure 579: % of patients with ≥2 points increase in Child-Pugh score (assessed at end of 48 weeks treatment)



G.3.3.2 Compensated cirrhosis (or advanced fibrosis)- HBeAg negative

Entecavir versus lamivudine (advanced fibrosis/cirrhosis)

Figure 580: % of patients with undetectable HBV DNA (<300copies/mL) (assessed at end of 48 weeks treatment)

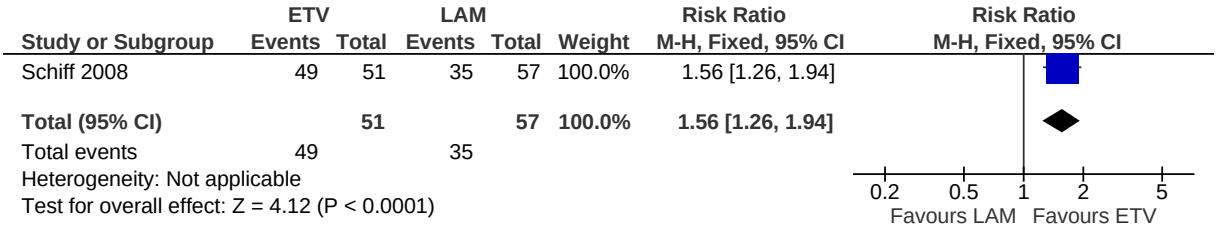
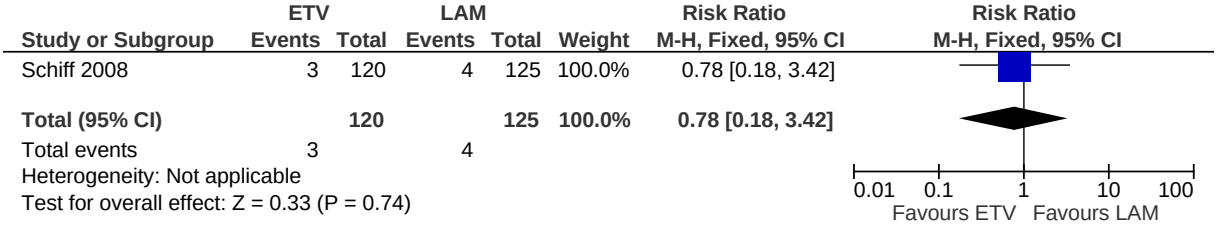


Figure 581: Mortality (assessed at end of 48 weeks treatment) (3 groups combined: HBeAg positive, negative and lamivudine refractory)



G.3.3.3 Compensated cirrhosis (or advanced fibrosis)- Lamivudine refractory patients

Entecavir versus lamivudine (advanced fibrosis/cirrhosis)

Figure 582: % of patients with undetectable HBV DNA (<300copies/mL) (assessed at end of 48 weeks treatment)

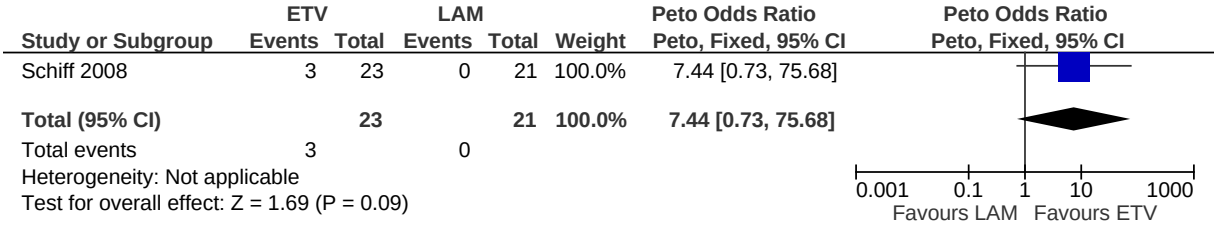
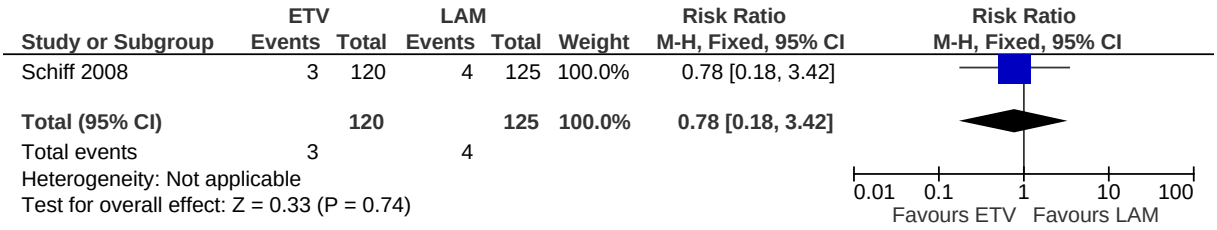


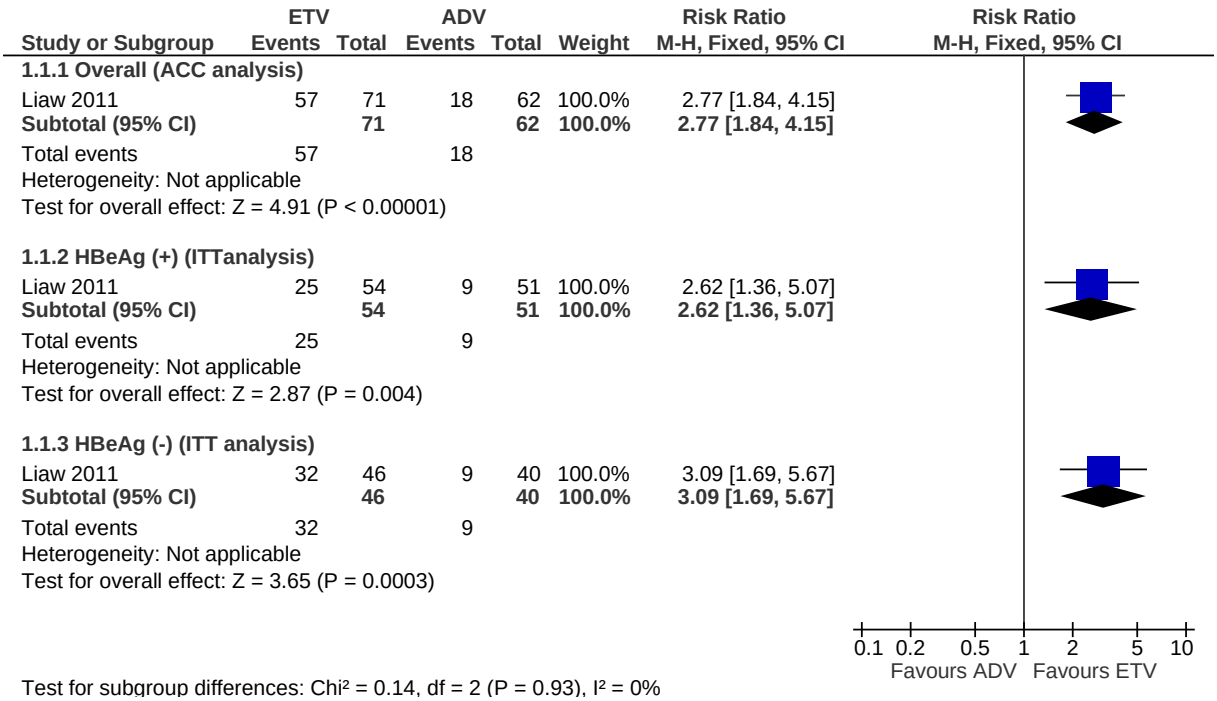
Figure 583: Mortality (assessed at end of 48 weeks treatment) (3 groups combined: HBeAg positive, negative and lamivudine refractory)



G.3.3.4 Decompensated cirrhosis – mixed HBeAg populations

Entecavir versus adefovir (decompensated cirrhosis)

Figure 584: % of patients with undetectable HBV DNA (assessed at end of 48 weeks treatment)



Test for subgroup differences: $Chi^2 = 0.14$, df = 2 (P = 0.93), $I^2 = 0\%$

Figure 585: % of patients with Child-Pugh score ≥2 points decrease (assessed at end of 48 weeks treatment)

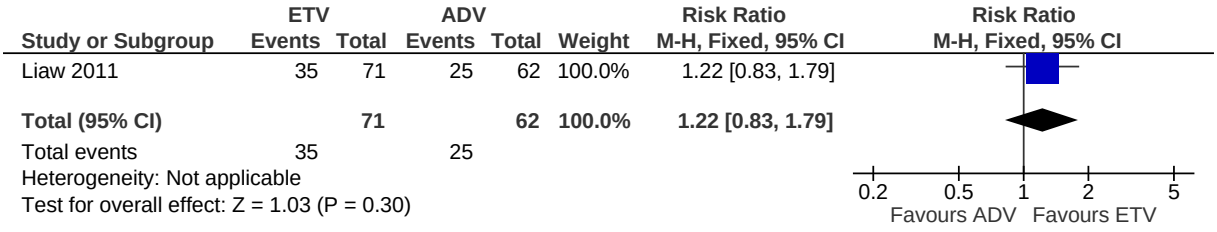


Figure 586: Log reduction of HBV DNA (assessed at end of 48 weeks treatment)

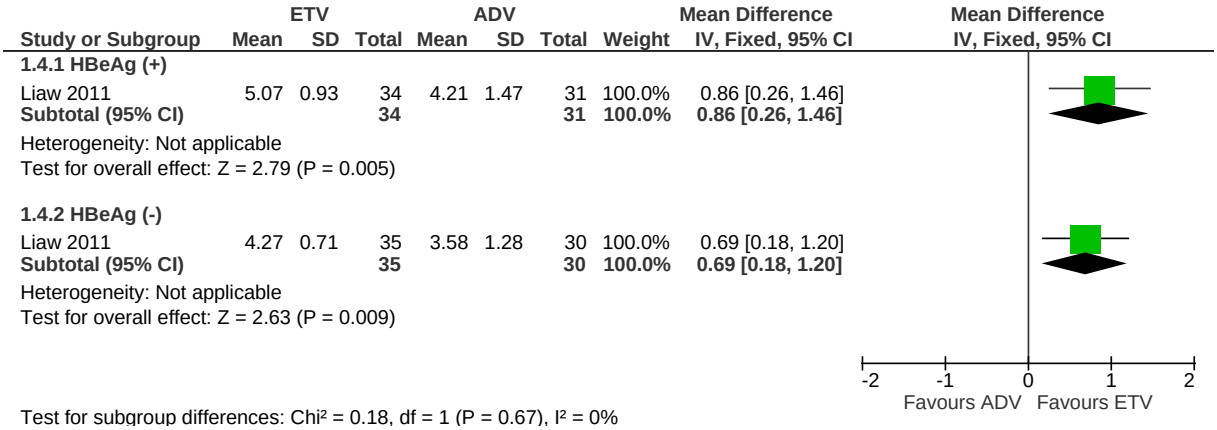


Figure 587: Resistance (assessed at end of 48 weeks treatment)

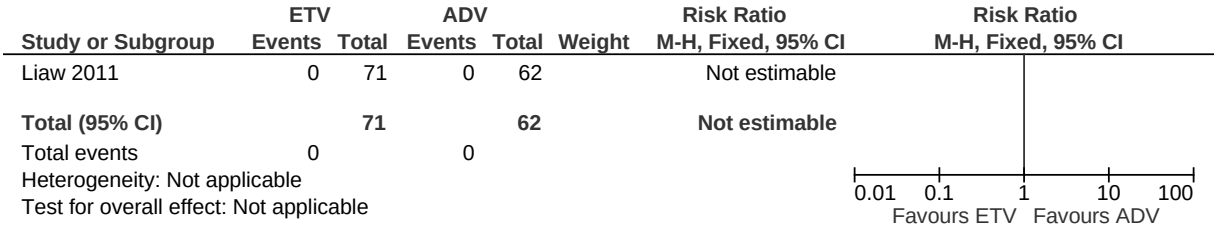


Figure 588: % of patients with incidence of hepatocellular carcinoma (assessed at end of 48 weeks treatment)

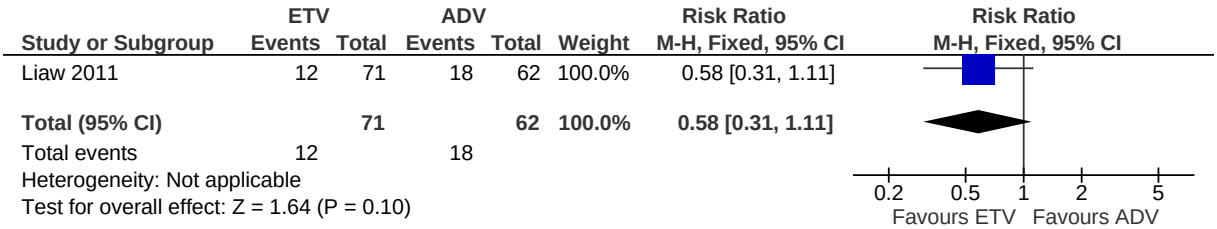


Figure 589: Mortality (assessed at end of 48 weeks treatment)

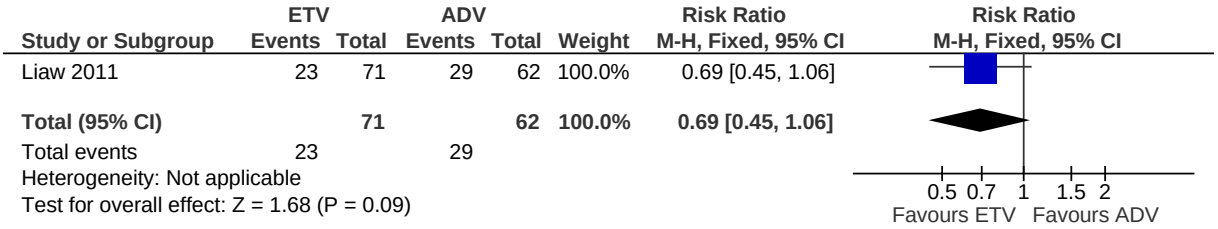


Figure 590: Liver transplantation

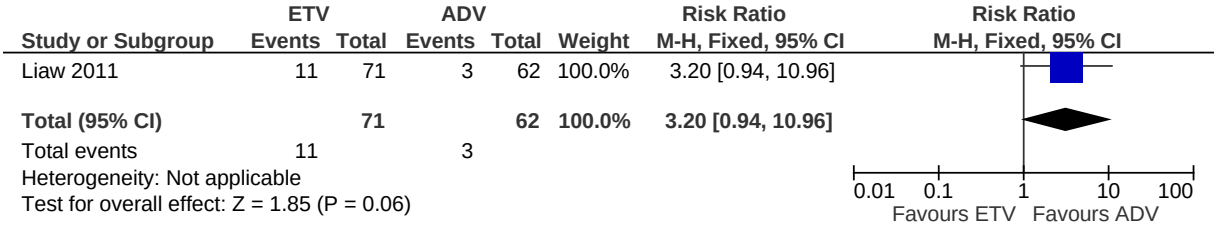
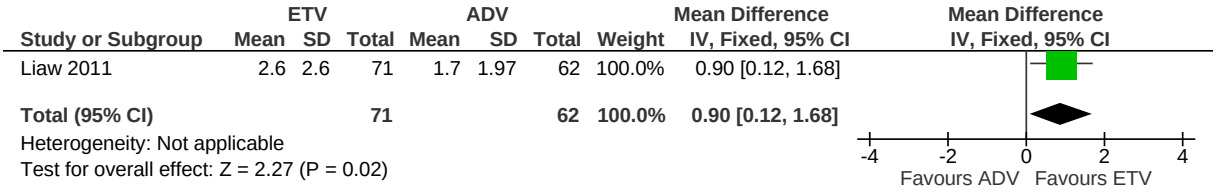


Figure 591: MELD score (change from baseline) (assessed at end of 48 weeks treatment)



Tenofovir plus Emtricitabine versus tenofovir (decompensated cirrhosis)

Figure 592: Liver transplantation (assessed at end of 48 weeks treatment)

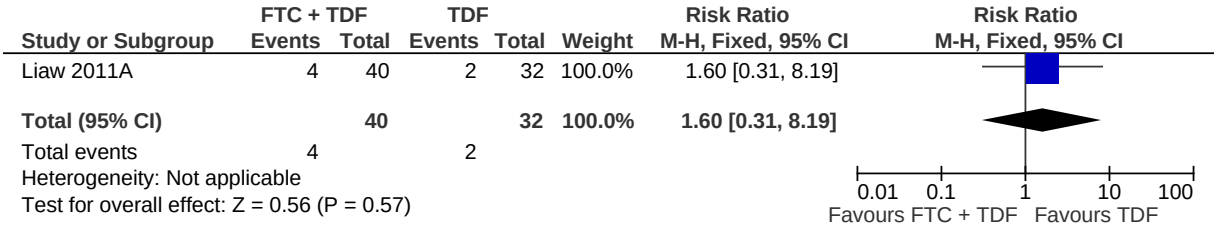


Figure 593: Mortality (assessed at end of 48 weeks treatment)

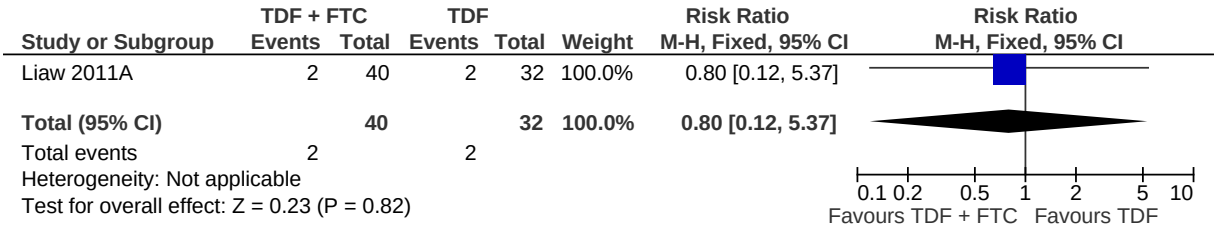


Figure 594: Incidence of hepatocellular carcinoma (assessed at end of 48 weeks treatment)

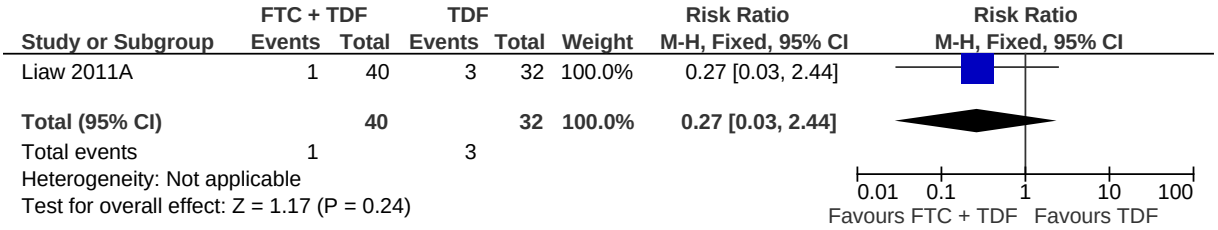


Figure 595: Resistance (assessed at end of 48 weeks treatment)

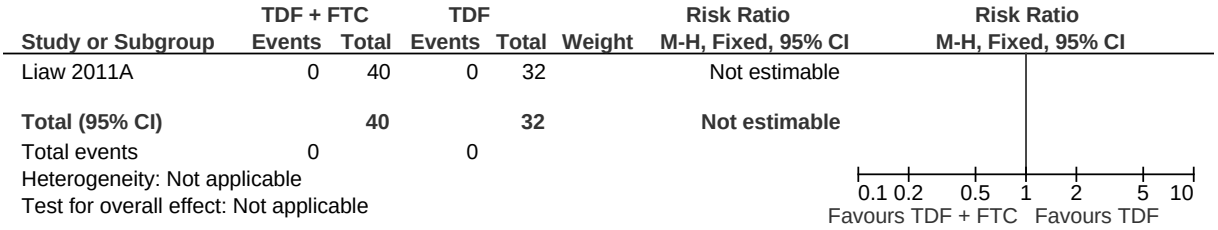


Figure 596: Log reduction of HBV DNA (assessed at end of 48 weeks treatment)

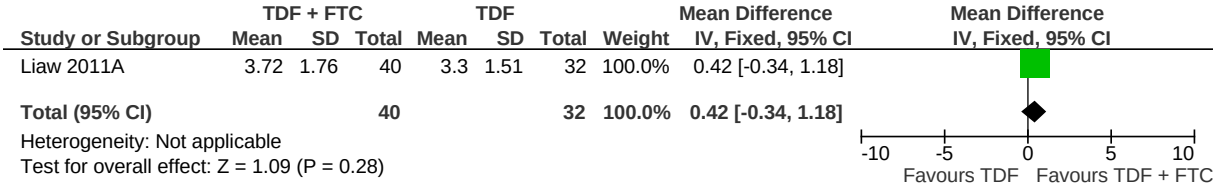


Figure 597: % of patients with undetectable HBV DNA (<400copies/mL) (assessed at end of 48 weeks treatment)

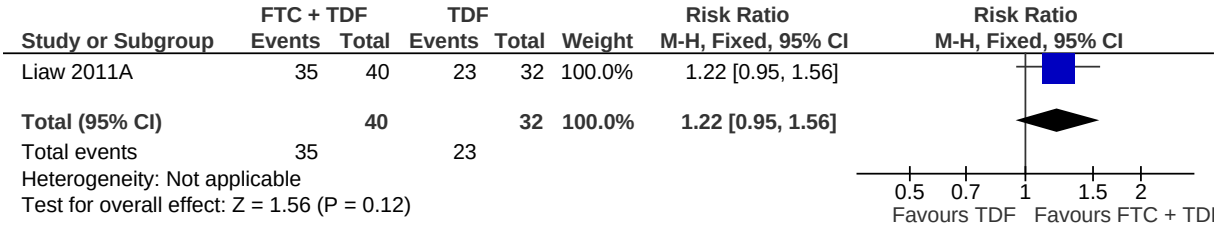


Figure 598: % of patients with Child-Pugh score≥2 point decrease (assessed at end of 48 weeks treatment)

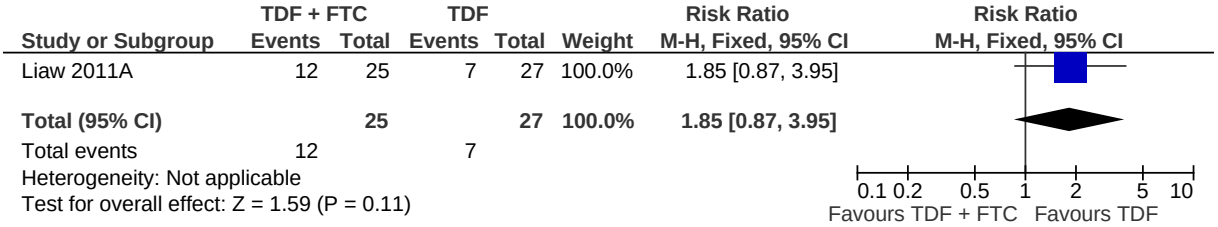


Figure 599: Complications – ascites

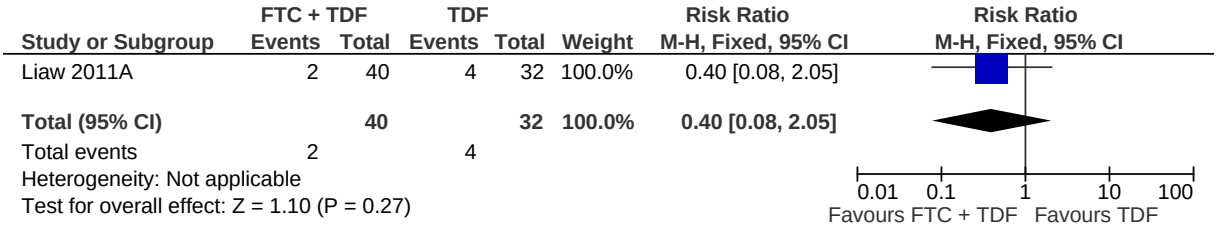
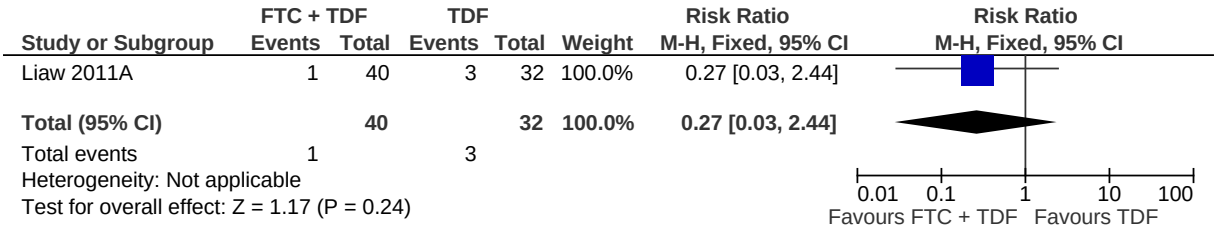


Figure 600: Complications - encephalopathy



Entecavir versus tenofovir (decompensated cirrhosis)

Figure 601: Liver transplantation (assessed at end of 48 weeks of treatment)

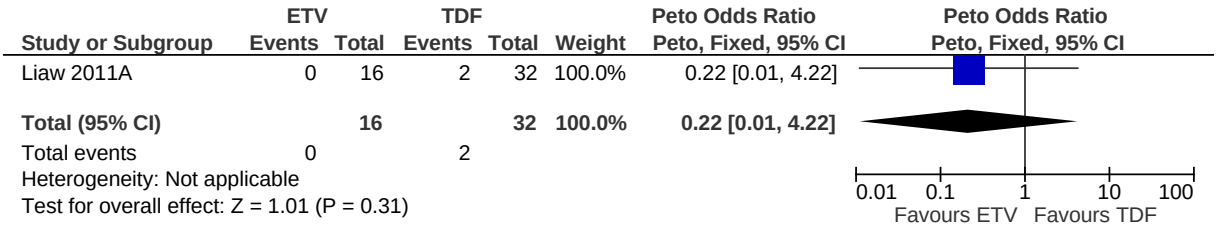


Figure 602: Mortality (assessed at end of 48 weeks of treatment)

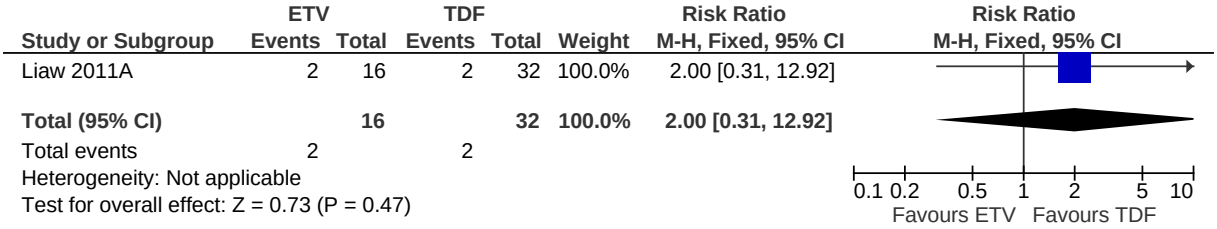


Figure 603: Incidence of hepatocellular carcinoma (assessed at end of 48 weeks of treatment)

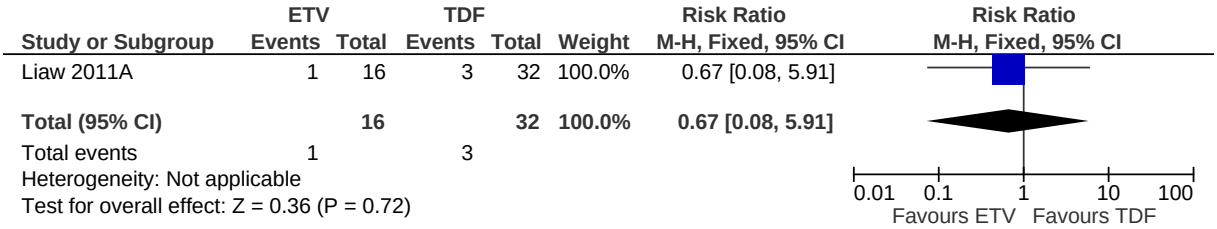


Figure 604: Resistance (assessed at end of 48 weeks of treatment)

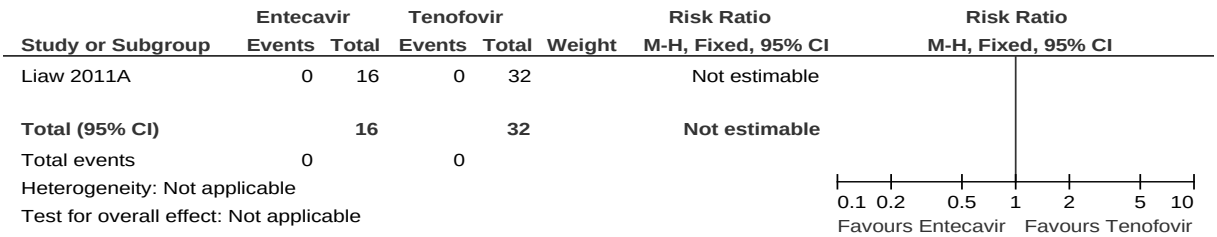


Figure 605: Log reduction of HBV DNA (assessed at end of 48 weeks of treatment)

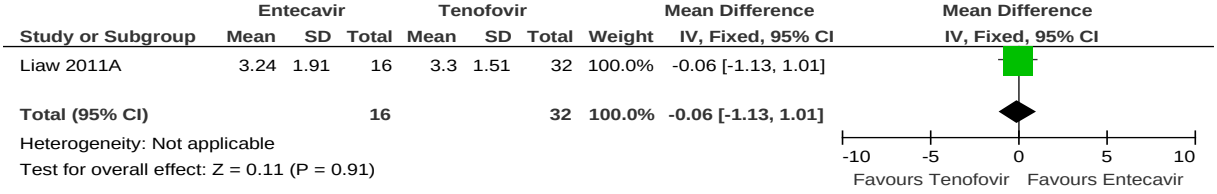


Figure 606: % of patients with undetectable HBV DNA (<400copies/mL) (assessed at end of 48 weeks treatment)

Study or Subgroup	Entecavir Events	Total	Tenofovir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Liaw 2011A	12	16	23	32	100.0%	1.04 [0.73, 1.49]
Total (95% CI)		**16**		**32**	**100.0%**	**1.04 [0.73, 1.49]**
Total events	12		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.81)

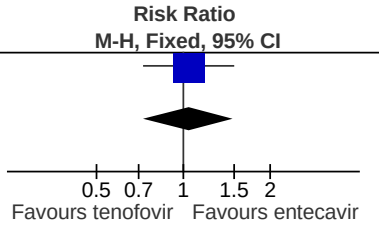


Figure 607: % of patients with Child-Pugh score≥2 point decrease (assessed at end of 48 weeks treatment)

Study or Subgroup	Entecavir Events	Total	Tenofovir Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Liaw 2011A	5	12	7	27	100.0%	1.61 [0.64, 4.05]
Total (95% CI)		**12**		**27**	**100.0%**	**1.61 [0.64, 4.05]**
Total events	5		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

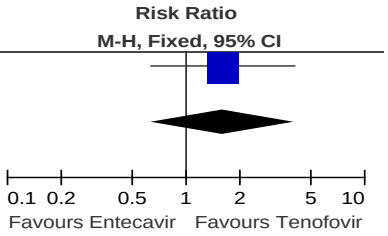


Figure 608: Complications – ascites (assessed at end of 48 weeks treatment)

Study or Subgroup	ETV Events	Total	TDF Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Liaw 2011A	4	16	4	32	100.0%	2.00 [0.57, 6.98]
Total (95% CI)		**16**		**32**	**100.0%**	**2.00 [0.57, 6.98]**
Total events	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.09 (P = 0.28)

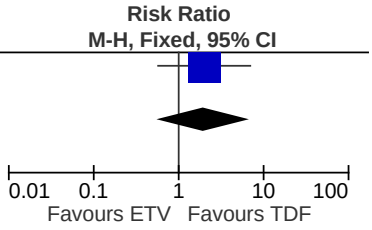
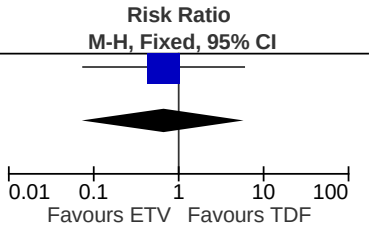


Figure 609: Complications – encephalopathy (assessed at end of 48 weeks treatment)

Study or Subgroup	ETV Events	Total	TDF Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Liaw 2011A	1	16	3	32	100.0%	0.67 [0.08, 5.91]
Total (95% CI)		**16**		**32**	**100.0%**	**0.67 [0.08, 5.91]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)



Tenofovir plus emtricitabine versus entecavir (decompensated cirrhosis)

Figure 610: Liver transplantation (assessed at end of 48 weeks of treatment)

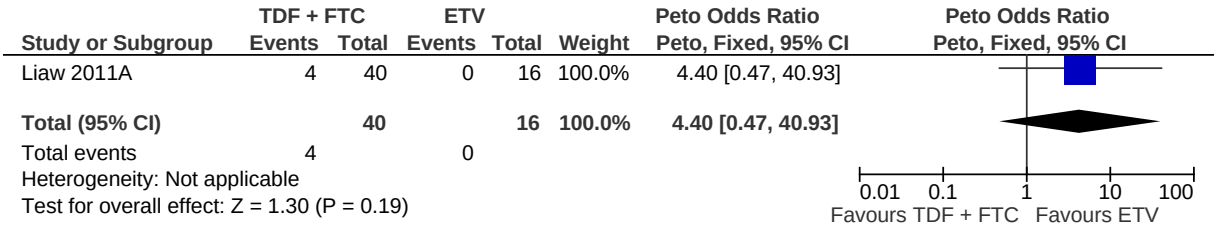


Figure 611: Mortality (assessed at end of 48 weeks of treatment)

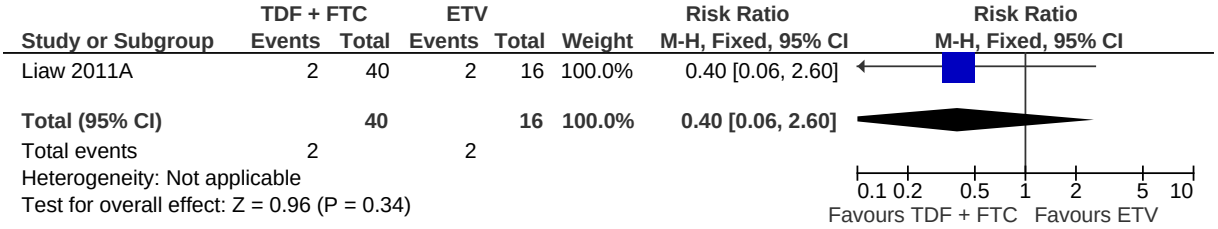


Figure 612: Incidence of hepatocellular carcinoma (assessed at end of 48 weeks of treatment)

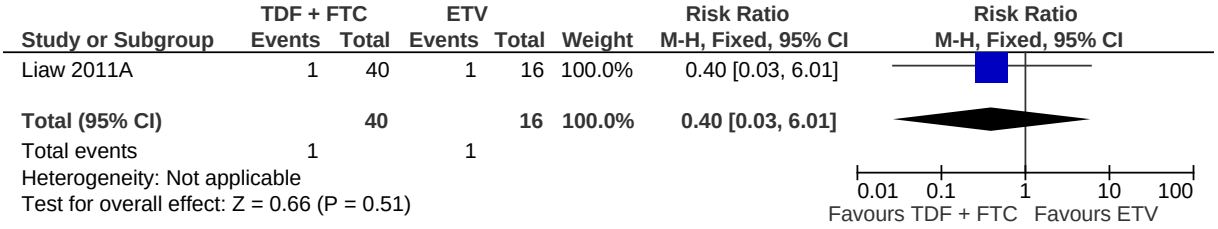


Figure 613: Resistance (assessed at end of 48 weeks of treatment)

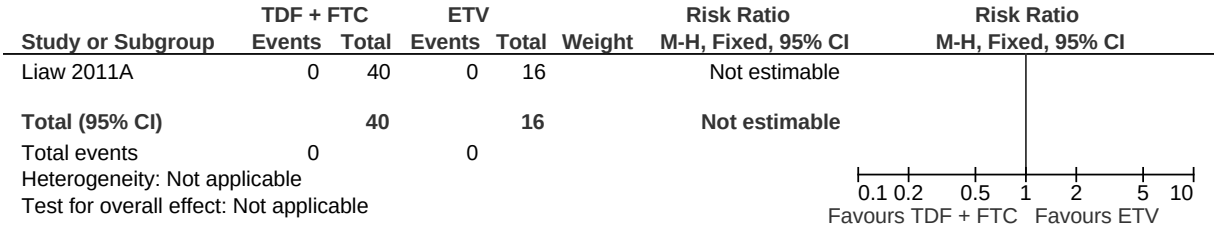


Figure 614: Log reduction of HBV DNA (assessed at end of 48 weeks of treatment)

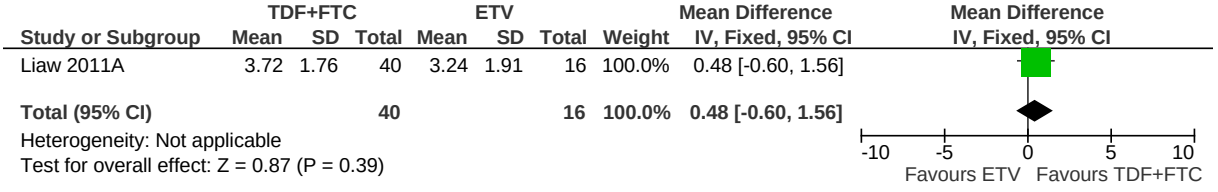


Figure 615: % of patients with undetectable HBV DNA (<400copies/mL) (assessed at end of 48 weeks treatment)

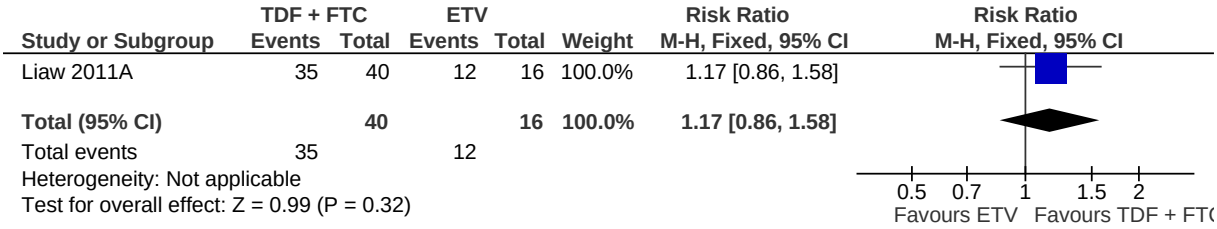


Figure 616: % of patients with Child-Pugh score≥2 point decrease (assessed at end of 48 weeks treatment)

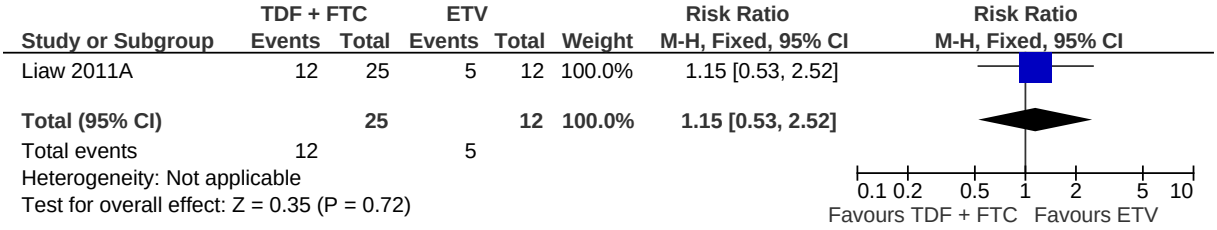


Figure 617: Complications – ascites

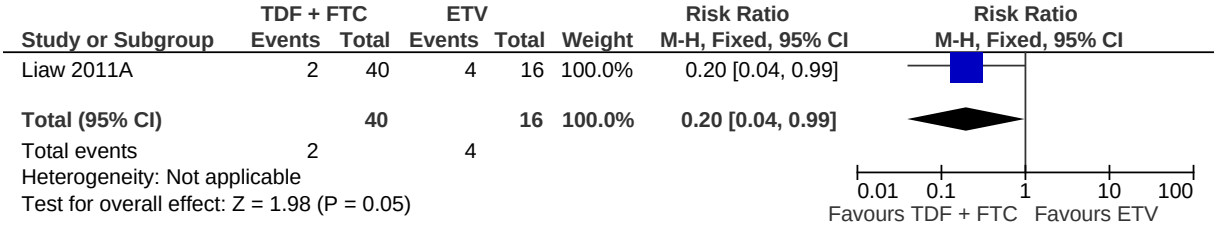
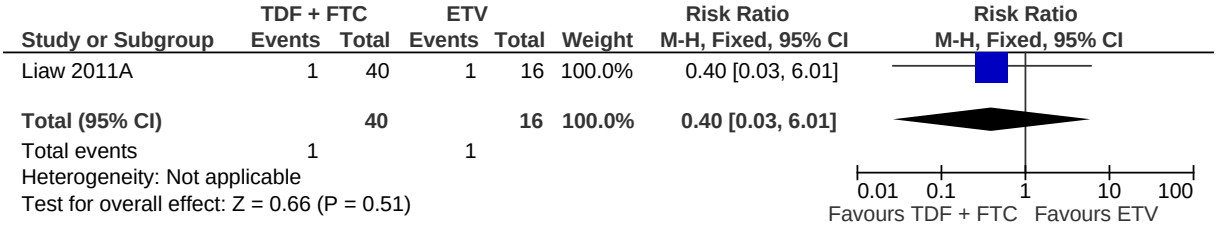


Figure 618: Complications – encephalopathy



G.3.4 Prophylactic treatment

G.3.4.1 Prophylactic entecavir vs. prophylactic lamivudine in HBsAg positive patients

Lymphoma patients undergoing chemotherapy

Figure 619: % patients with HBV reactivation at end of treatment – 24 weeks after completion of chemotherapy (non-RCT)

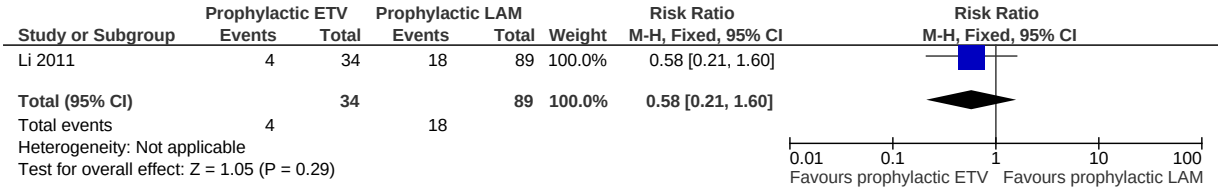


Figure 620: % patients with hepatitis at end of treatment – 24 weeks after completion of chemotherapy (non-RCT)

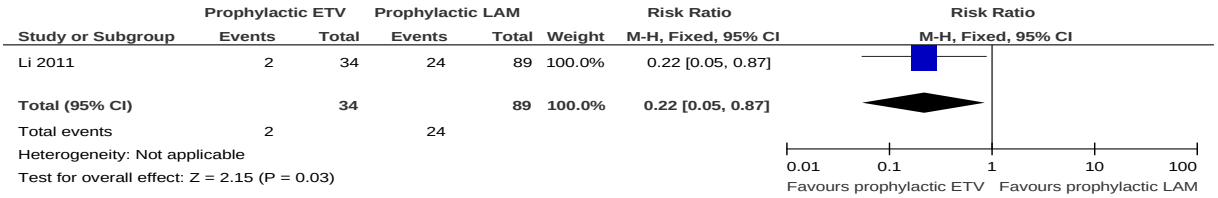


Figure 621: % patients with hepatitis due to HBV at end of treatment – 24 weeks after completion of chemotherapy (non-RCT)

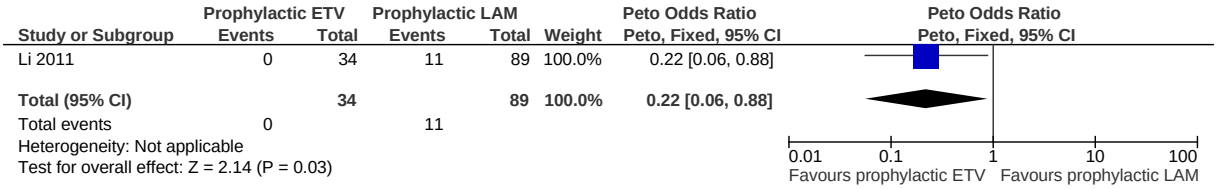


Figure 622: % patients with hepatic failure (severe) at end of treatment – 24 weeks after completion of chemotherapy (non-RCT)

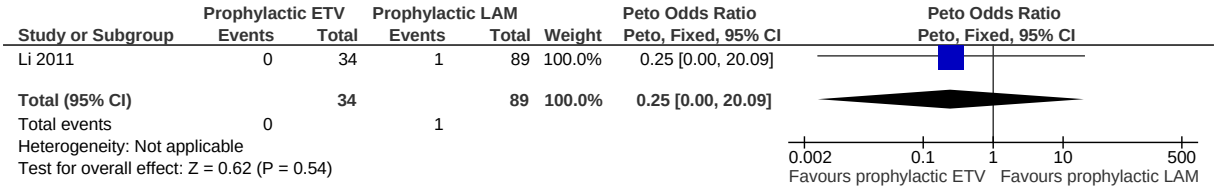


Figure 623: All-cause mortality at end of treatment – 24 weeks after completion of chemotherapy (non-RCT)

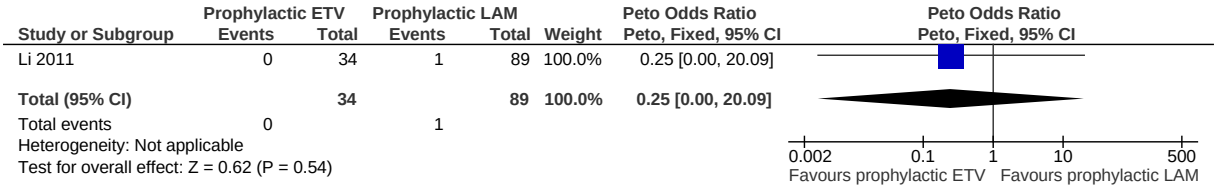


Figure 624: Resistance at end of treatment – 24 weeks after completion of chemotherapy (non-RCT)

G.3.4.2 Prophylactic lamivudine vs. no prophylactic lamivudine in HBsAg positive patients

Figure 625: % breast cancer patients undergoing chemotherapy with HBV reactivation at 8 weeks after completion of chemotherapy (RCT)

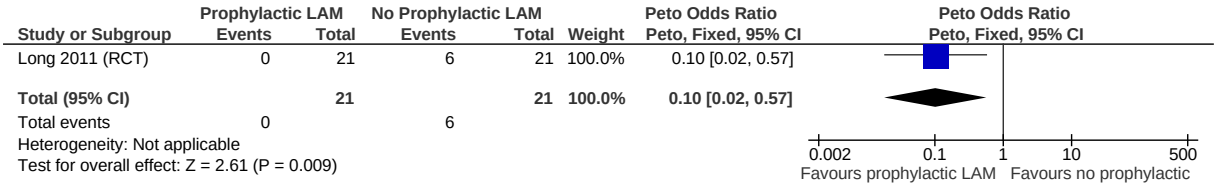


Figure 626: % breast cancer patients undergoing chemotherapy with hepatitis at 8 weeks after completion of chemotherapy (RCT)

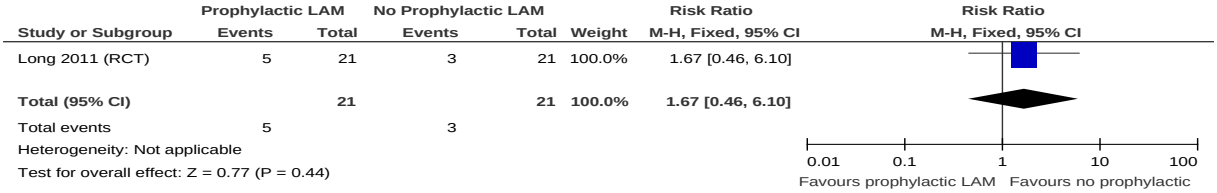


Figure 627: % cancer patients undergoing chemotherapy with hepatitis at 8 weeks after completion of immunosuppressive treatment (non-RCTs)

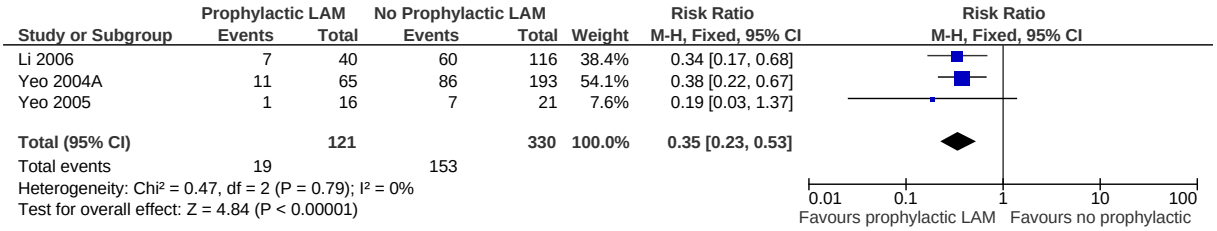


Figure 628: % patients undergoing stem cell (bone marrow) transplantation with hepatitis at 52 weeks after completion of immunosuppressive treatment (non-RCTs)

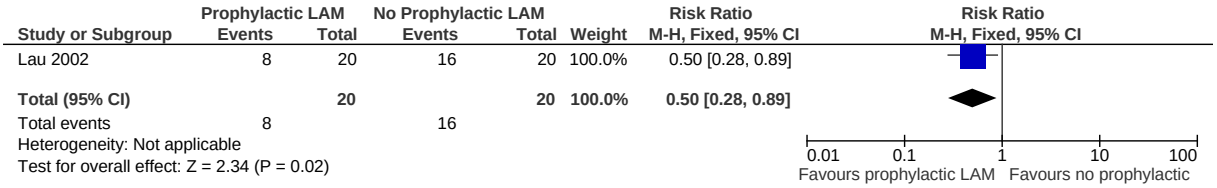


Figure 629: All-cause mortality in breast cancer patients undergoing chemotherapy at 8 weeks after completion of chemotherapy (RCT)

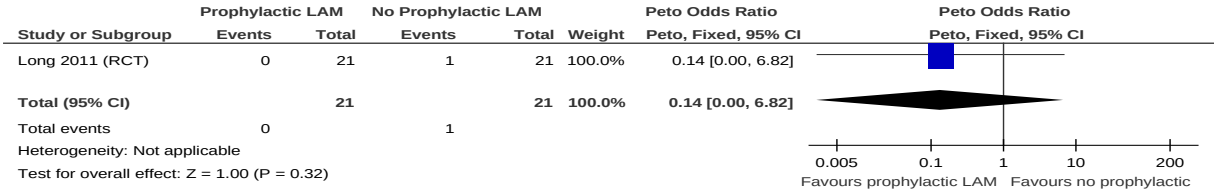


Figure 630: All-cause mortality, in cancer patients undergoing chemotherapy at 8 weeks after completion of immunosuppressive treatment (non-RCTs)

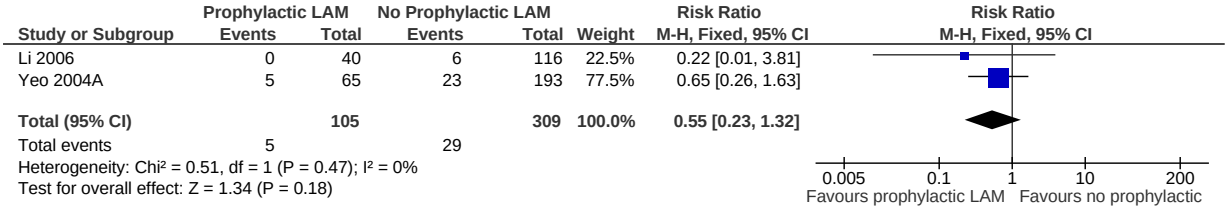


Figure 631: All-cause mortality, in patients undergoing stem cell (bone marrow) transplantation at 24 and 52 weeks after completion of immunosuppressive treatment (non-RCTs)

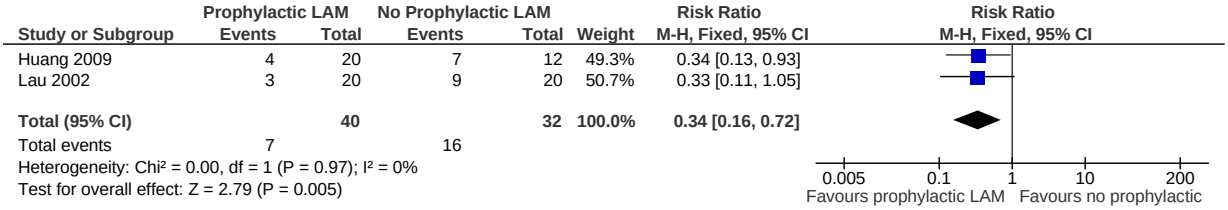


Figure 632: % breast cancer patients undergoing chemotherapy with hepatitis due to HBV at 8 weeks after completion of chemotherapy (RCT)

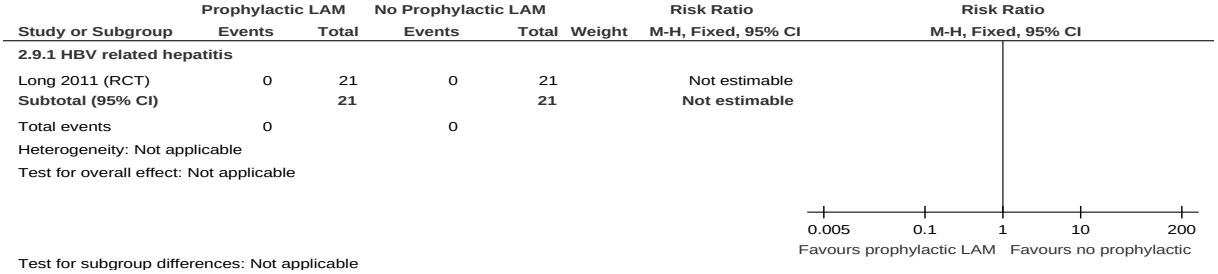


Figure 633: % cancer patients undergoing chemotherapy with hepatitis due to HBV at 8 weeks after completion of immunosuppressive treatment (non-RCTs)

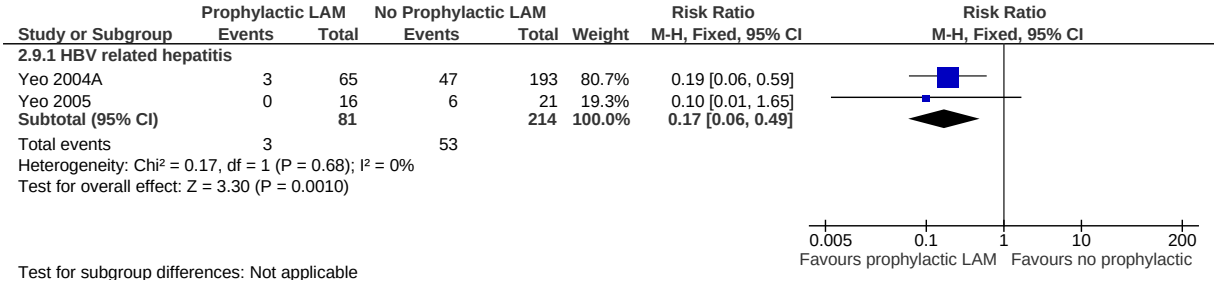


Figure 634: % patients undergoing stem cell (bone marrow) transplantation with hepatitis due to HBV at 24 and 52 weeks after completion of immunosuppressive treatment (non-RCTs)

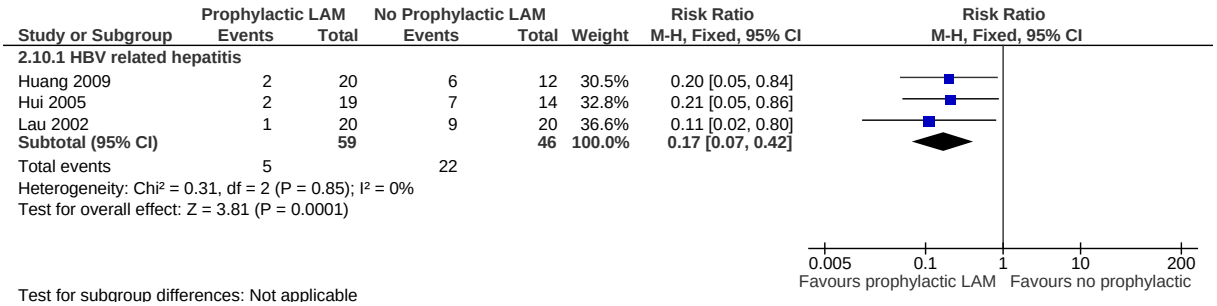


Figure 635: Mortality due to HBV reactivation in breast cancer patients undergoing chemotherapy at 8 weeks after completion of chemotherapy (RCT)

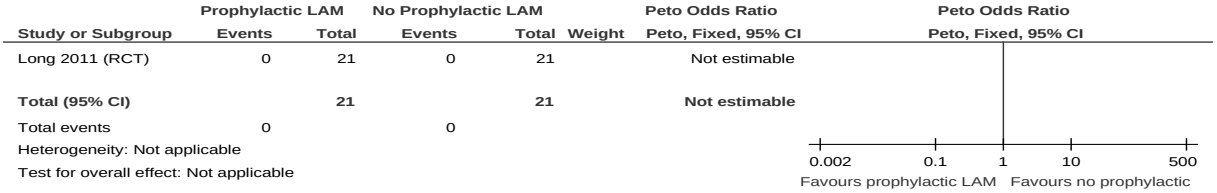


Figure 636: Mortality due to HBV reactivation, in cancer patients undergoing chemotherapy at 8 weeks after completion of immunosuppressive treatment (non-RCTs)

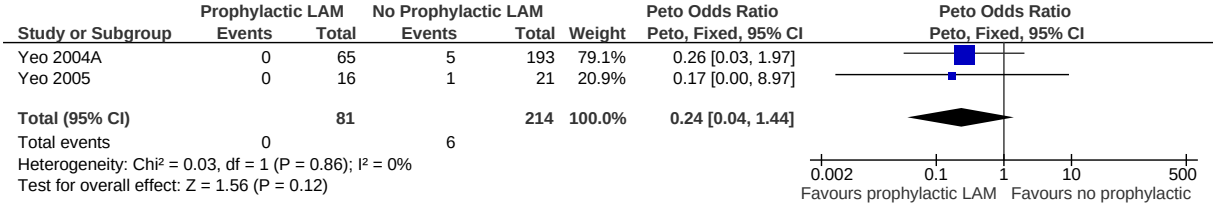


Figure 637: Mortality due to HBV reactivation, in patients undergoing stem cell (bone marrow) transplantation at 24 and 52 weeks after completion of immunosuppressive treatment (non-RCTs)

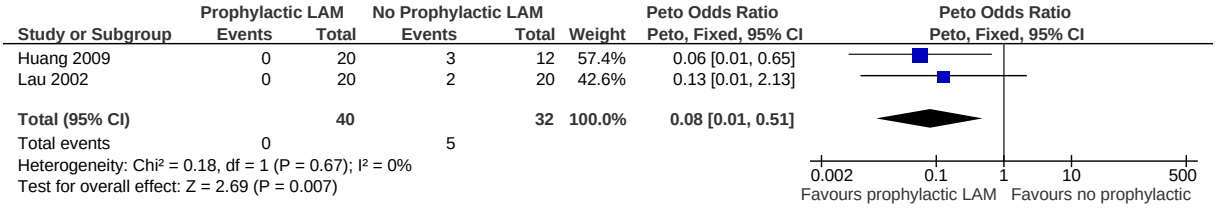


Figure 638: Resistance in cancer patients undergoing chemotherapy (monitored at least 12 weeks after completion of immunosuppressive treatment) (non-RCTs)

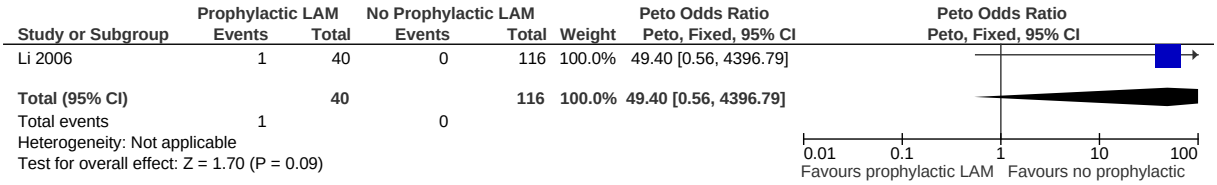
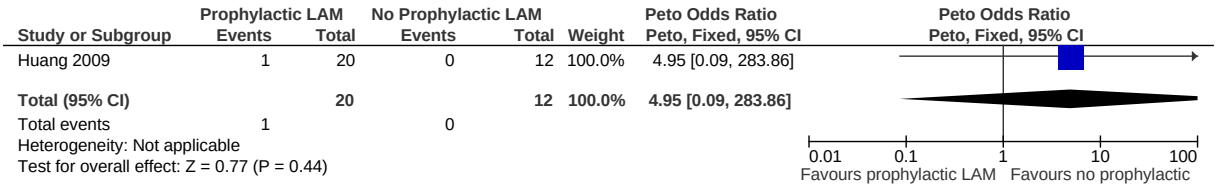


Figure 639: Resistance in patients undergoing stem cell (bone marrow) transplantation at 24 weeks after completion of immunosuppressive treatment (non-RCT)



G.3.4.3 Prophylactic lamivudine vs. preemptive lamivudine (start LAM when there was HBV reactivation, after starting immunosuppressive therapy) in HBsAg positive patients

Figure 640: % cancer patients (lymphoma and HBV related hepatocellular carcinoma) undergoing chemotherapy (including transarterial chemo-lipiolisation) with HBV reactivation at minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy

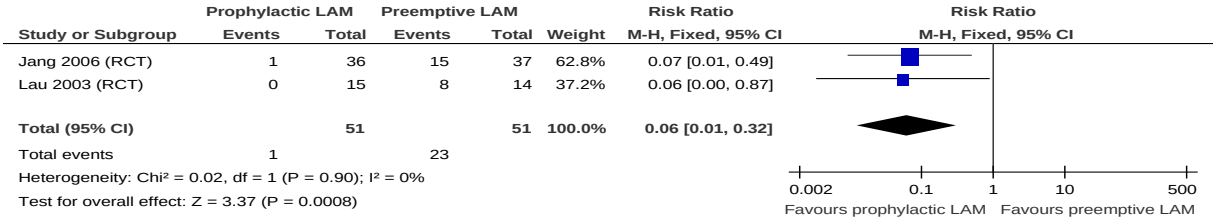


Figure 641: % HBV related hepatocellular carcinoma patients undergoing transarterial chemo-lipiolisation with hepatitis at 52 weeks after completion of immunosuppressive therapy

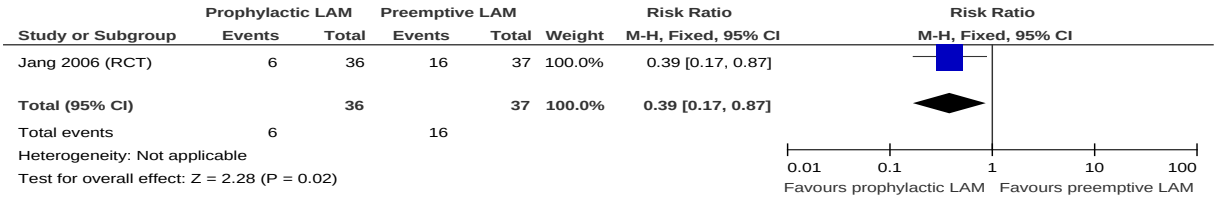


Figure 642: All-cause mortality in cancer patients (lymphoma and HBV related hepatocellular carcinoma) undergoing chemotherapy (including transarterial chemo-lipiolisation) at minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy

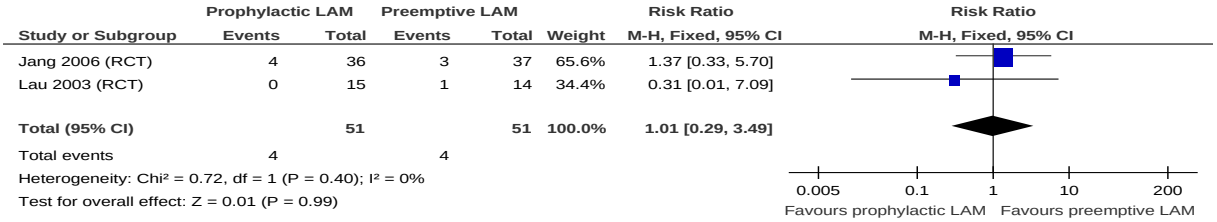


Figure 643: % cancer patients (lymphoma and HBV related hepatocellular carcinoma) undergoing chemotherapy (including transarterial chemo-lipiolisation) with hepatitis due to HBV at minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy

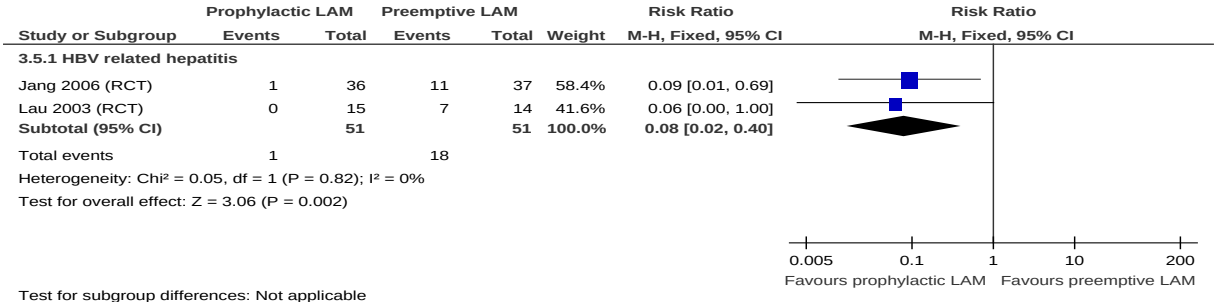


Figure 644: % lymphoma patients undergoing chemotherapy with hepatic failure at minimum 6 weeks after completion of chemotherapy

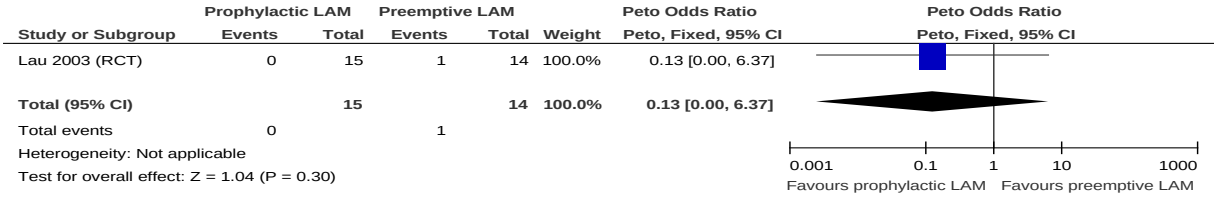


Figure 645: Mortality due to HBV reactivation/hepatitis/hepatic failure, in cancer patients (lymphoma and HBV related hepatocellular carcinoma) undergoing chemotherapy (including transarterial chemo-lipiolisation) at minimum 6 weeks to 52 weeks after completion of chemotherapy/immunosuppressive therapy

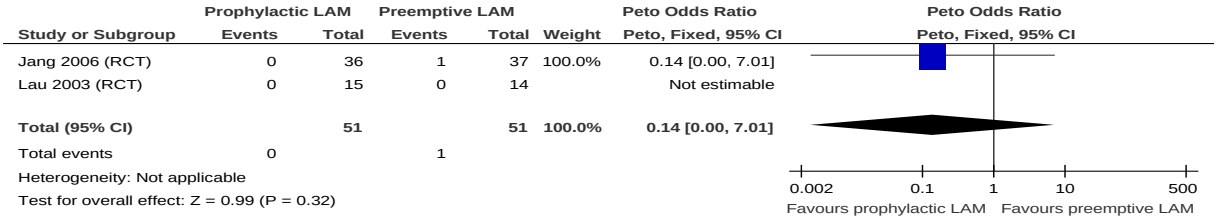


Figure 646: % HBV related hepatocellular carcinoma patients undergoing transarterial chemo-lipiolisation patients with hepatic decompensation at 52 weeks after completion of immunosuppressive therapy

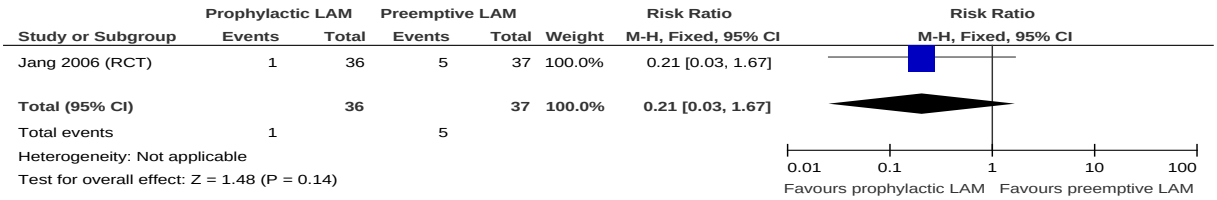
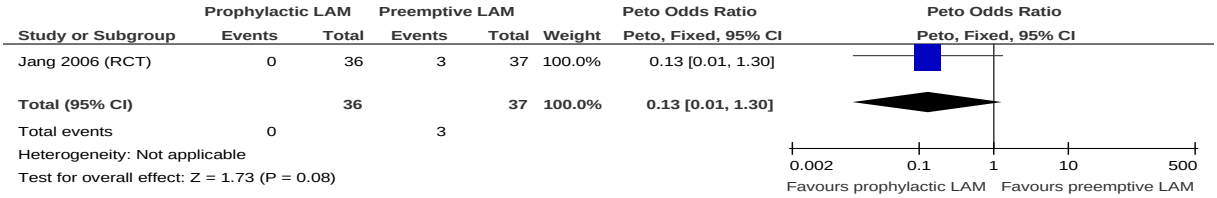


Figure 647: % HBV related hepatocellular carcinoma patients undergoing transarterial chemo-lipiolisation patients with hepatic decompensation due to HBV reactivation at 52 weeks after completion of immunosuppressive therapy



G.3.4.4 Prophylactic lamivudine vs. therapeutic lamivudine (start LAM only when there was elevation of ALT (hepatitis) and continued until hepatitis resolved, after starting immunosuppressive therapy) in HBsAg positive patients

Figure 648: % non-hodgkin's lymphoma patients undergoing chemotherapy with HBV reactivation, during lamivudine treatment

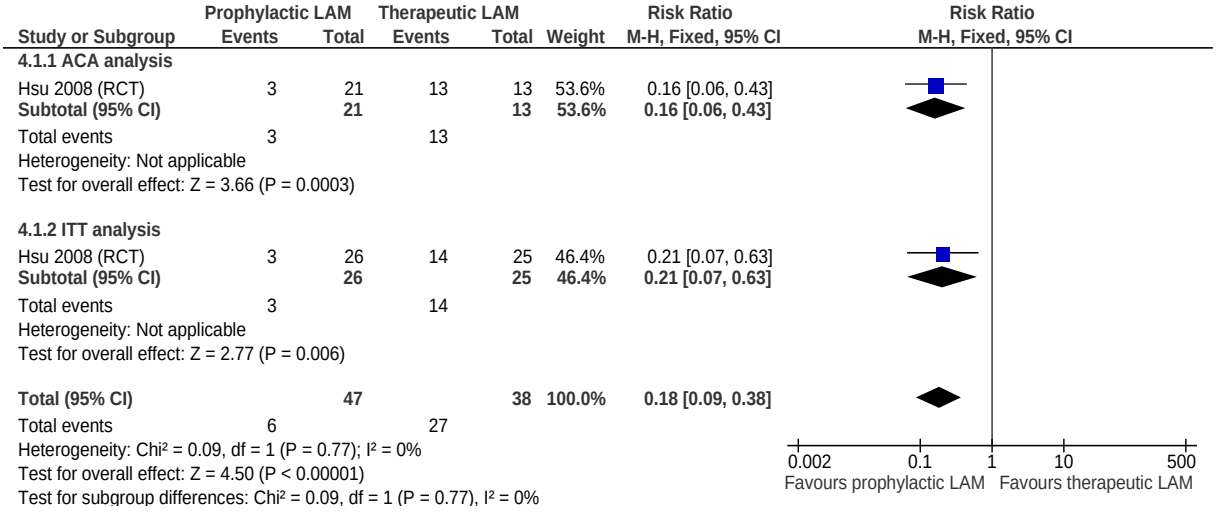


Figure 649: % non-hodgkin's lymphoma patients undergoing chemotherapy with hepatitis during lamivudine treatment

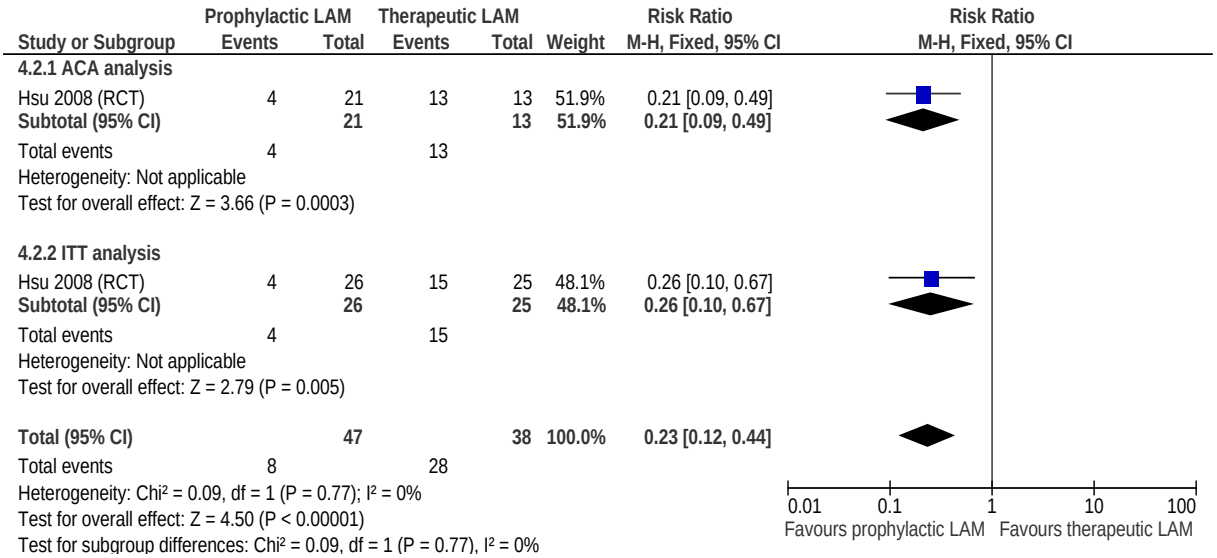


Figure 650: % non-hodgkin's lymphoma patients undergoing chemotherapy with hepatitis due to HBV during lamivudine treatment

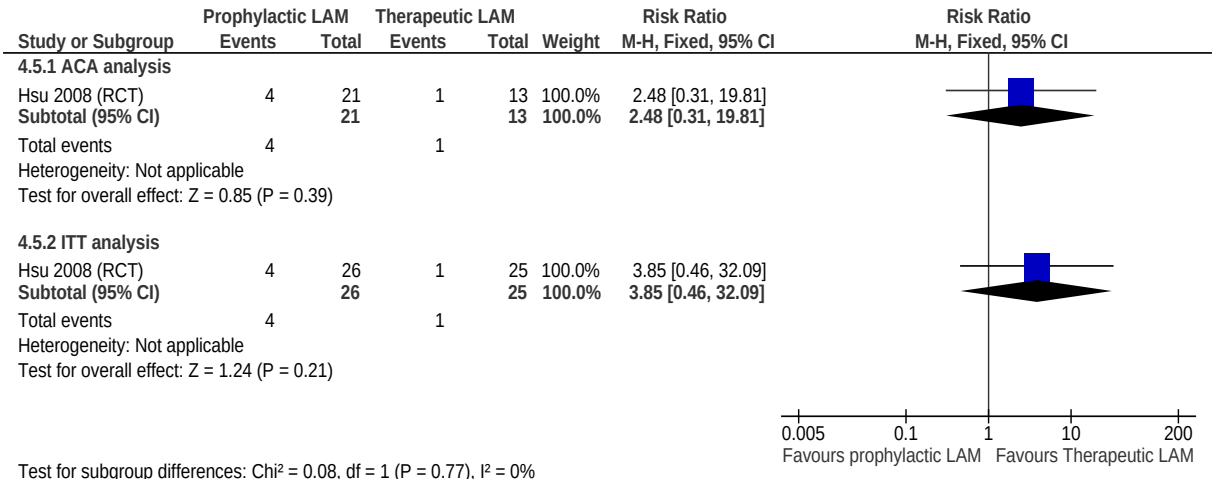


Figure 651: % non-hodgkin's lymphoma patients undergoing chemotherapy with HBV reactivation, at 52 weeks of ending chemotherapy

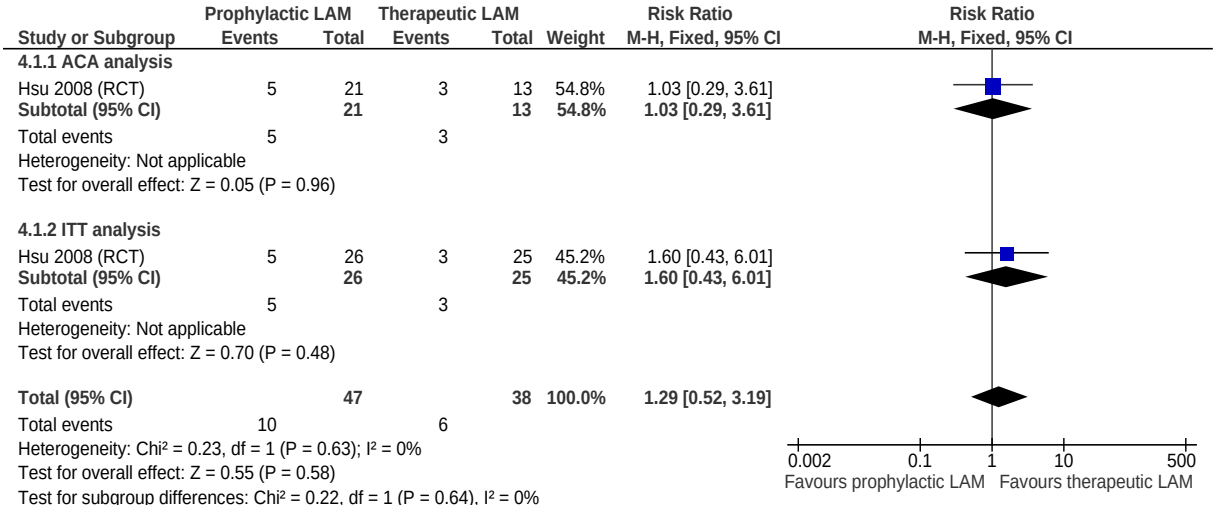


Figure 652: % non-hodgkin's lymphoma patients undergoing chemotherapy with hepatitis at 52 weeks of ending chemotherapy

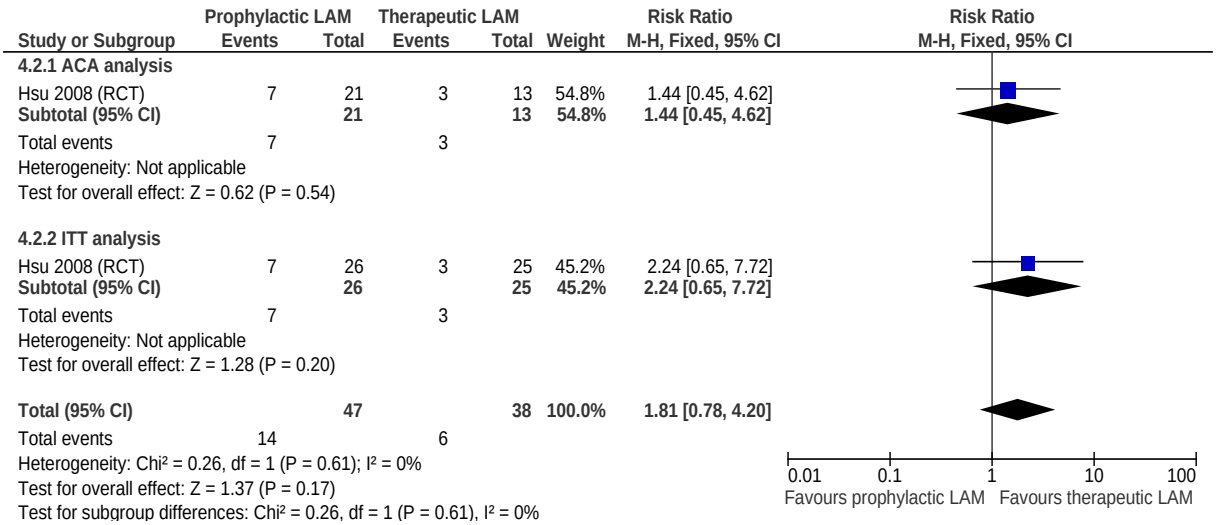


Figure 653: % non-hodgkin's lymphoma patients undergoing chemotherapy with hepatitis due to HBV at 52 weeks of ending chemotherapy

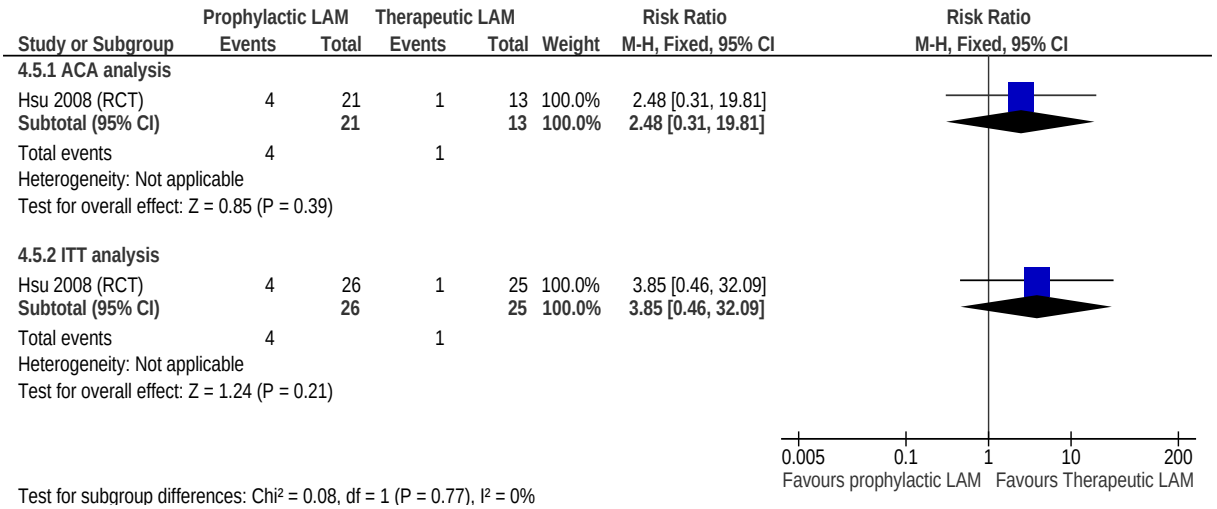


Figure 654: Mortality due to HBV reactivation/hepatitis/hepatic failure, in non-hodgkin's lymphoma patients undergoing chemotherapy at 52 weeks of ending chemotherapy

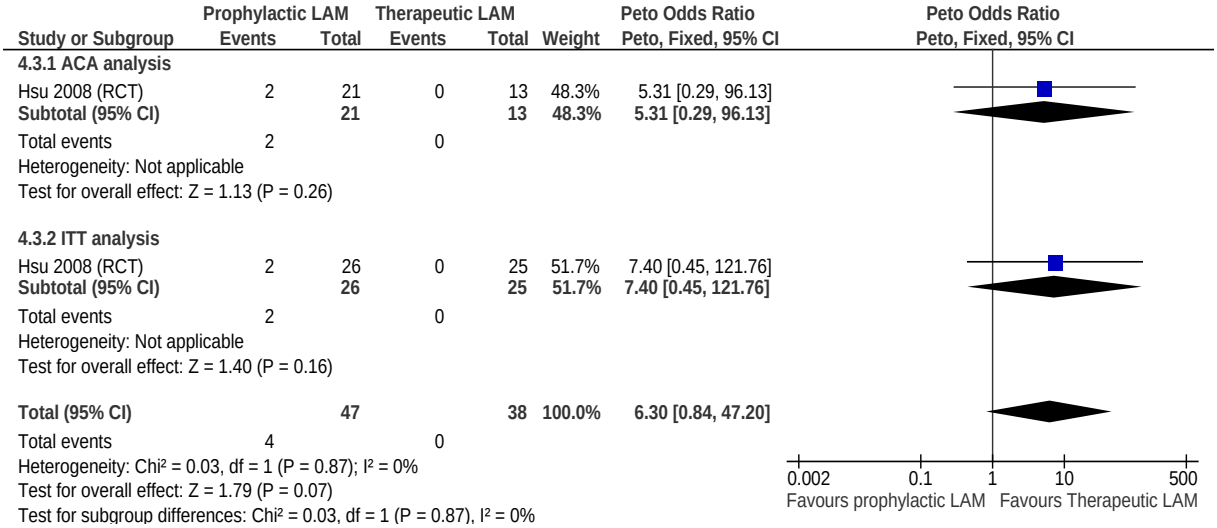
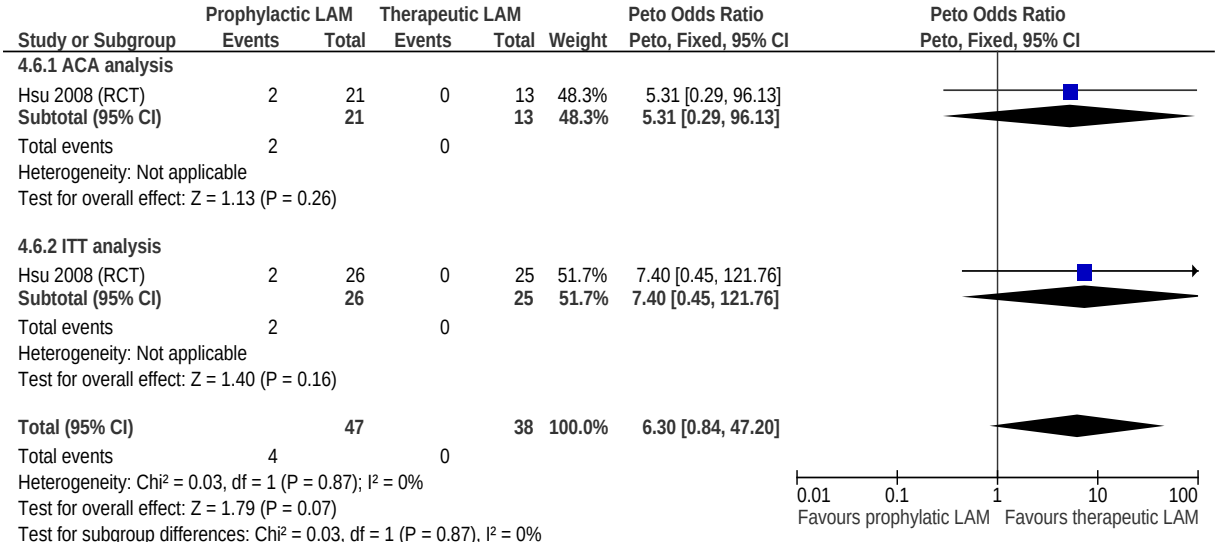


Figure 655: Resistance in non-hodgkin's lymphoma patients undergoing chemotherapy at 52 weeks of ending chemotherapy



G.3.4.5 Comparison of pre-emptive lamivudine therapy (starting lamivudine only when there was HBV DNA and/or ALT elevation and/or significant hepatitis after starting immunosuppressive therapy) versus no therapy, according to causes of immunosuppression

Figure 656: Overall mortality , in kidney allograft recipients undergoing chemotherapy (end of follow up- mean 82 (SD 58) months after transplantation)

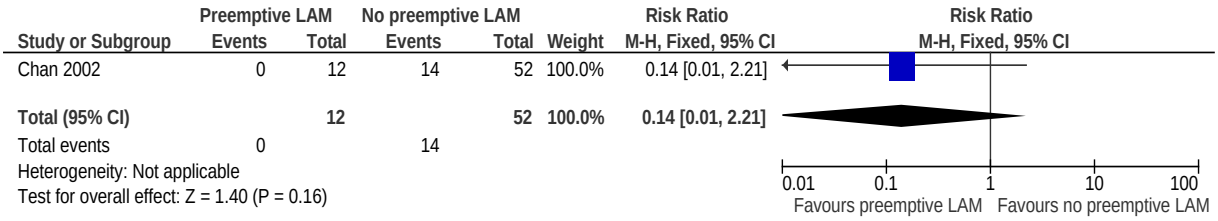
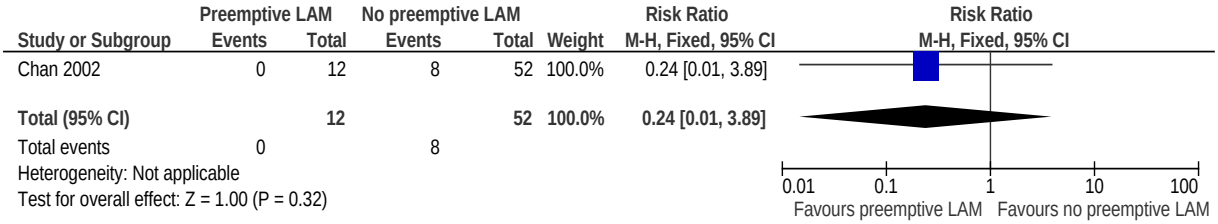


Figure 657: Mortality due to liver complications , in kidney allograft recipients undergoing chemotherapy (end of follow up- mean 82 (SD 58) months after transplantation)



G.3.5 Pregnant women

G.3.5.1 Comparison of lamivudine (vaccine+ HBIG) versus placebo (vaccine+ HBIG)

Figure 658: HBsAg seropositivity at birth (newborns)

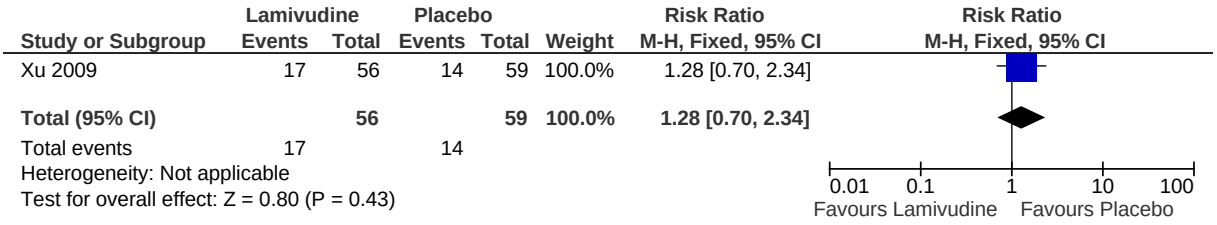


Figure 659: HBsAg seropositivity at birth (newborns) (OBS)

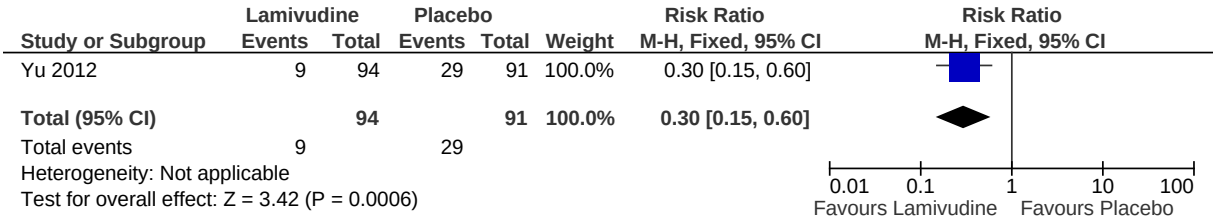


Figure 660: HBsAg seropositivity at 1 month (newborns) (OBS)

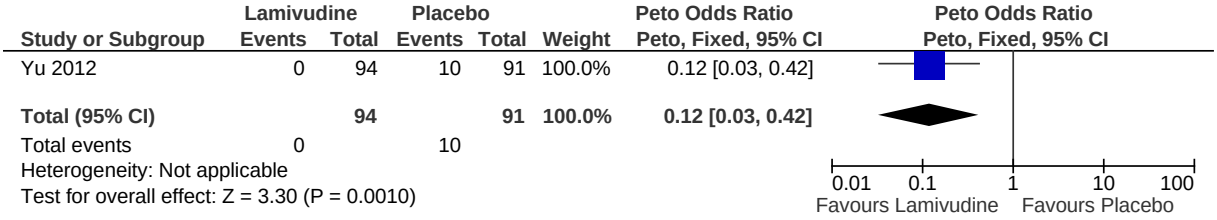


Figure 661: HBsAg seropositivity at week 12 (infants)

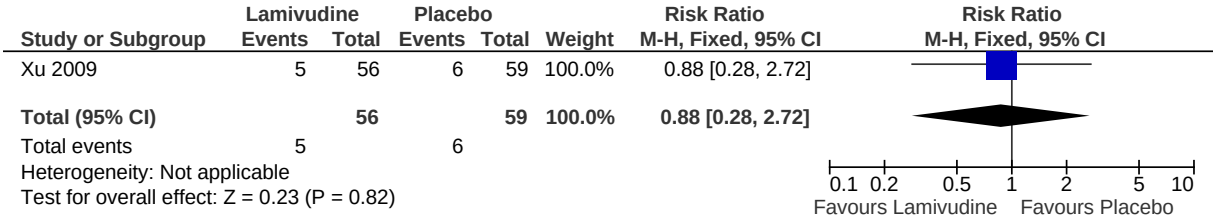


Figure 662: HBsAg seropositivity at week 28 (infants)

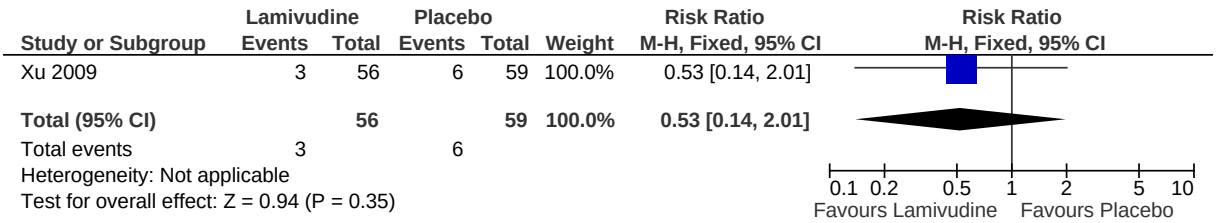


Figure 663: HBsAg seropositivity at week 52 (infants)

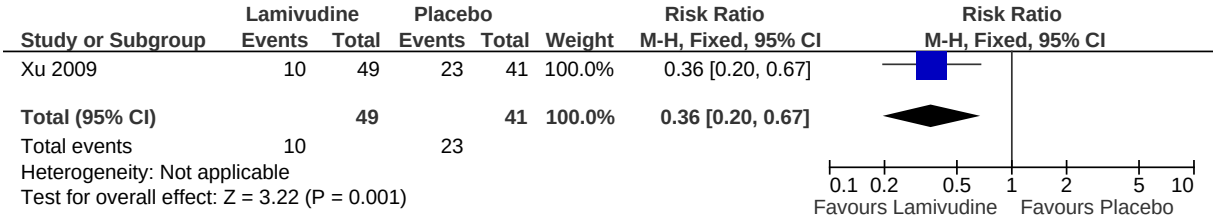


Figure 664: HBsAg seropositivity at week 52 (infants) (OBS)

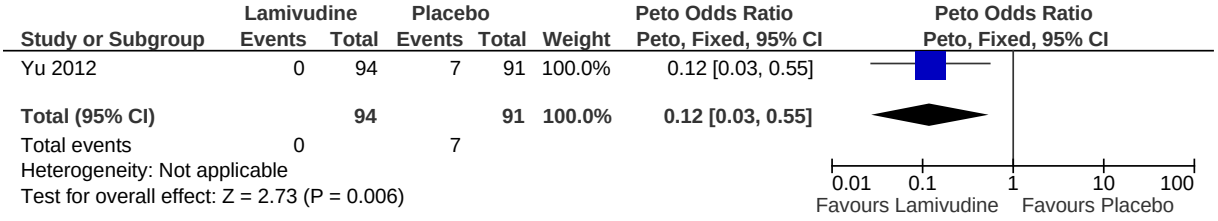


Figure 665: HBV DNA positivity at birth (newborns)

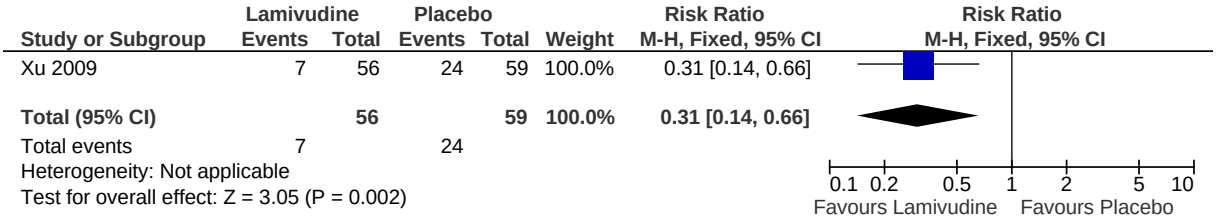


Figure 666: HBV DNA positivity at 1 month (newborns) (OBS)

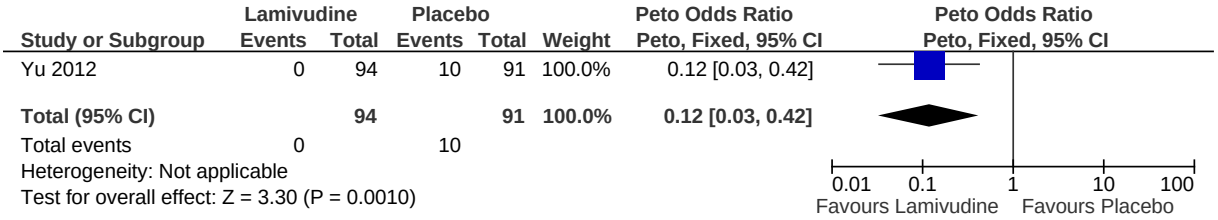


Figure 667: HBV DNA positivity at week 12 (infants)

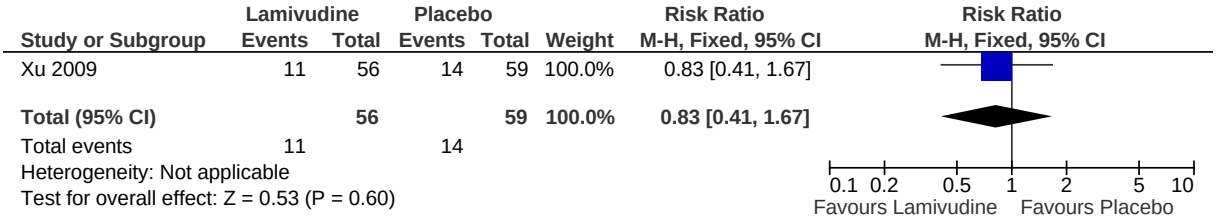


Figure 668: HBV DNA positivity at week 28 (infants)

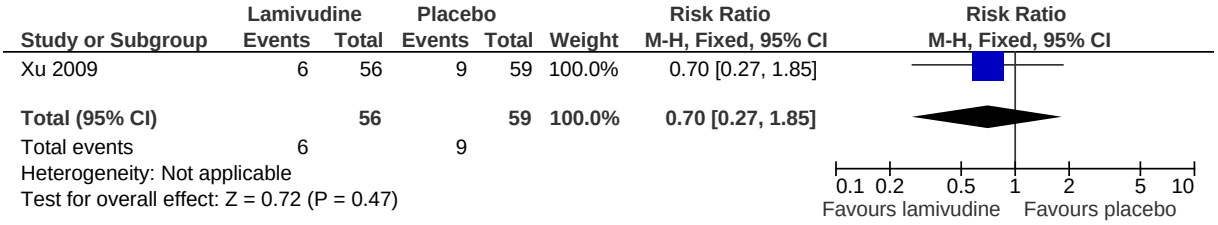


Figure 669: HBV DNA positivity at week 52 (infants)

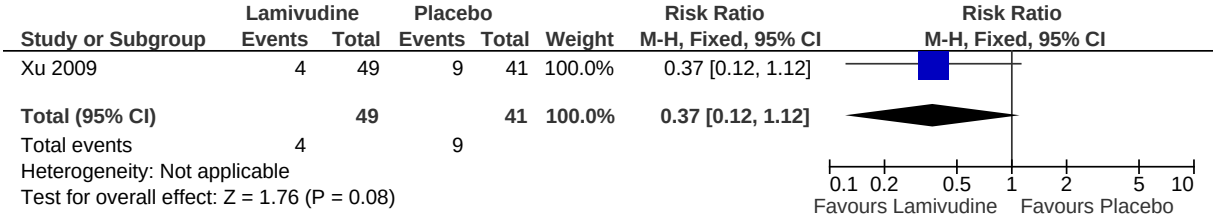


Figure 670: HBV DNA positivity at 12 months (infants) (OBS)

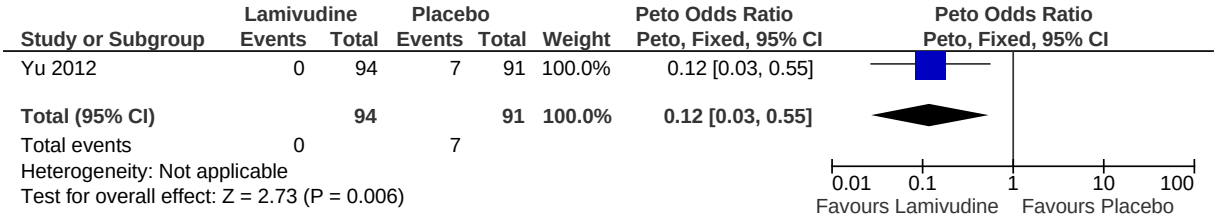


Figure 671: Maternal undetectable HBV DNA (before delivery) (OBS)

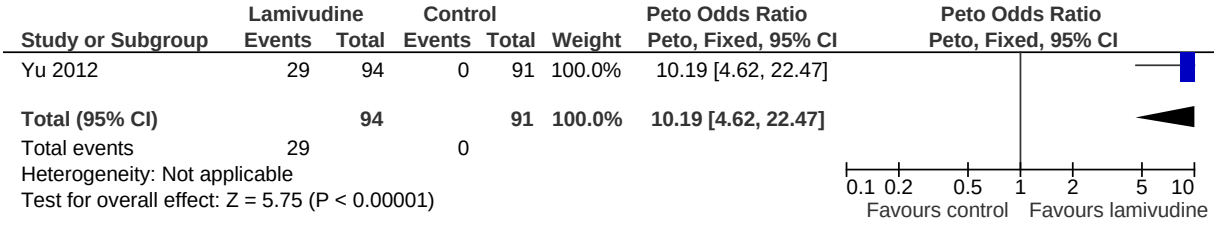


Figure 672: Maternal log HBV DNA (before delivery) (OBS)

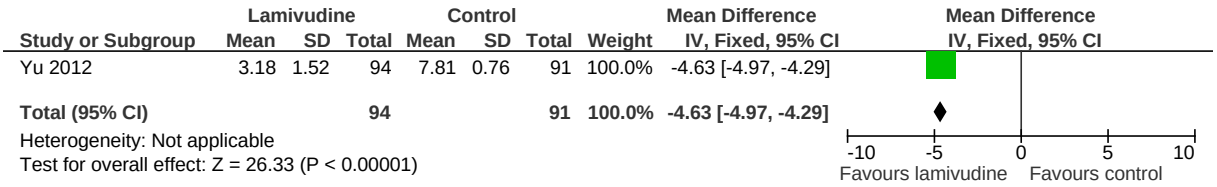


Figure 673: Infants adverse events

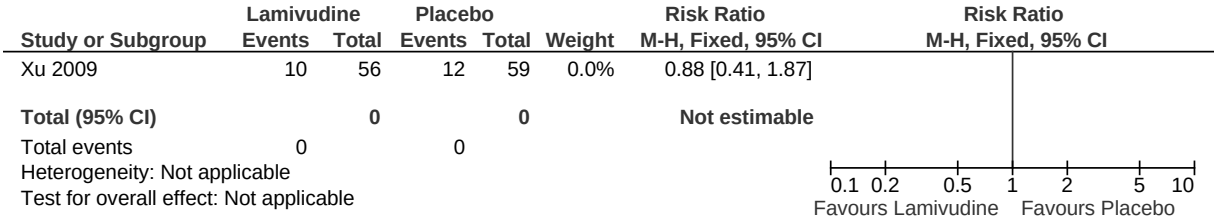


Figure 674: Infants serious adverse events

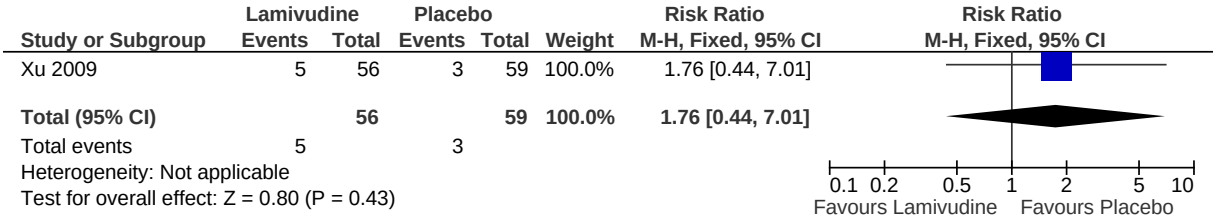


Figure 675: Maternal serious adverse events

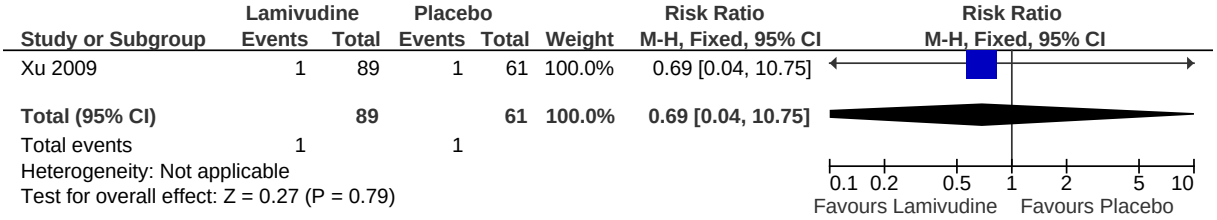


Figure 676: Maternal adverse events

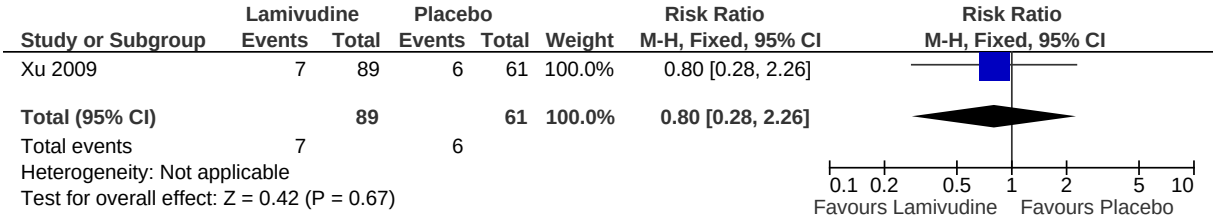


Figure 677: postpartum haemorrhage (OBS)

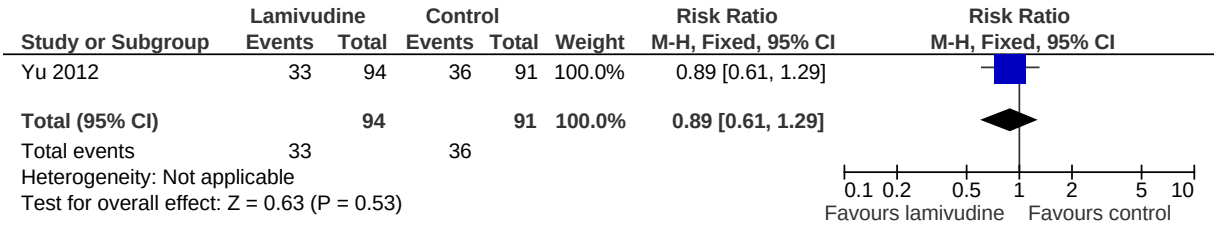


Figure 678: caesarean section (OBS)

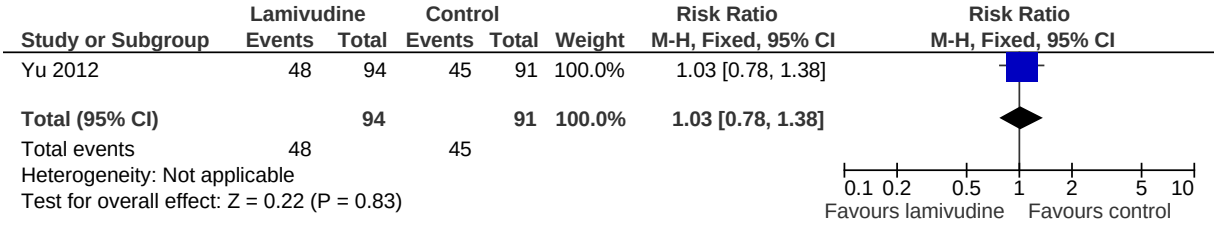


Figure 679: preterm birth (OBS)

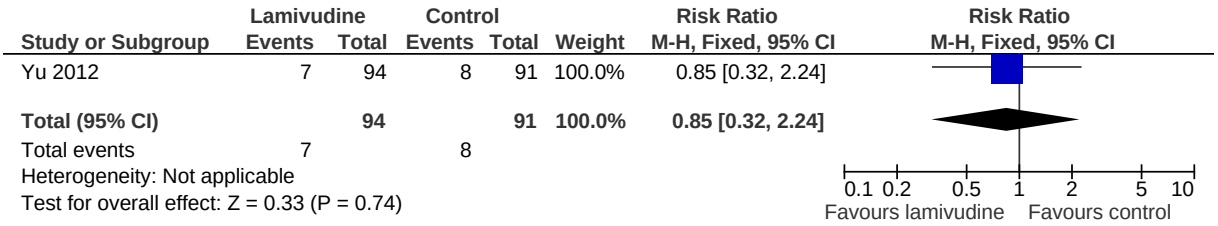


Figure 680: neonatal asphyxia (OBS)

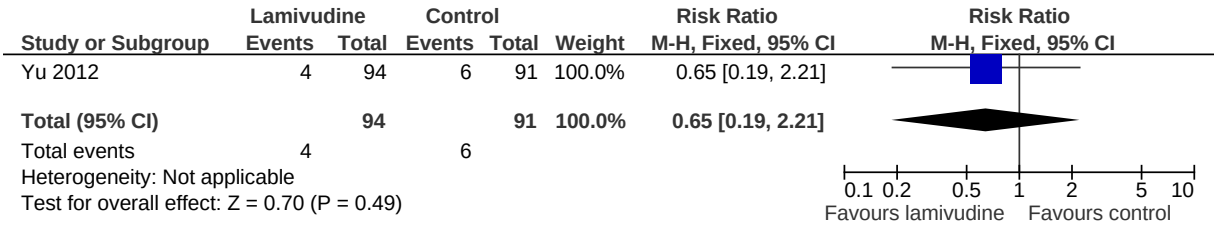
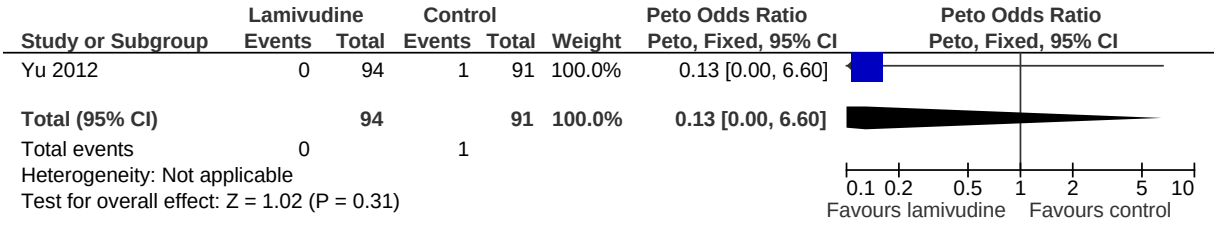


Figure 681: malformation (OBS)



G.3.5.2 Comparison of lamivudine (no vaccine) versus HBIG (no vaccine)

Figure 682: HBsAg seropositivity at birth (newborns)

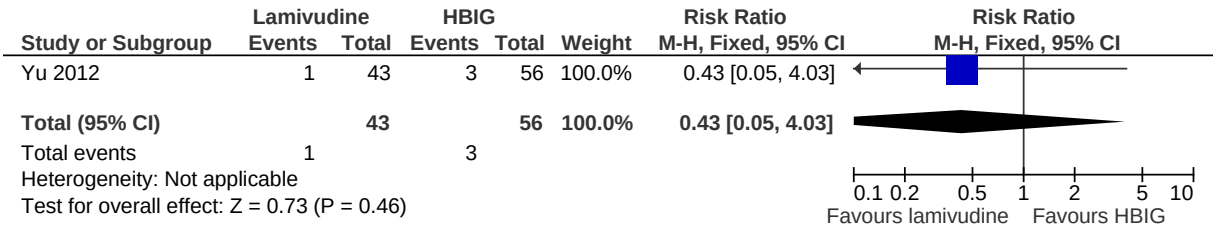


Figure 683: HBeAg seropositivity at birth (newborns)

Study or Subgroup	Lamivudine Events	Lamivudine Total	HBIG Events	HBIG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2012	7	43	7	56	100.0%	1.30 [0.49, 3.43]
Total (95% CI)		**43**		**56**	**100.0%**	**1.30 [0.49, 3.43]**
Total events	7		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.59)

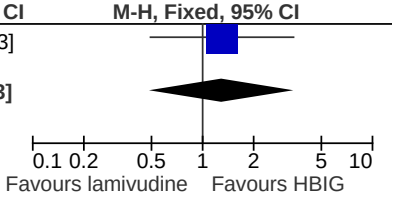


Figure 684: HBV DNA positivity at birth (newborns)

Study or Subgroup	Lamivudine Events	Lamivudine Total	HBIG Events	HBIG Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2012	7	43	9	56	100.0%	1.01 [0.41, 2.50]
Total (95% CI)		**43**		**56**	**100.0%**	**1.01 [0.41, 2.50]**
Total events	7		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)

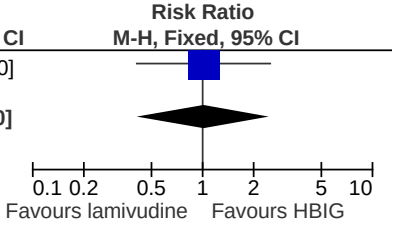
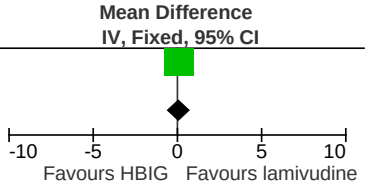


Figure 685: maternal HBV DNA reduction (after admin of agents)

Study or Subgroup	Lamivudine Mean	Lamivudine SD	Lamivudine Total	HBIG Mean	HBIG SD	HBIG Total	Weight	Mean Difference IV, Fixed, 95% CI
Yu 2012	2.16	1.27	43	2.09	2.28	56	100.0%	0.07 [-0.64, 0.78]
Total (95% CI)			**43**			**56**	**100.0%**	**0.07 [-0.64, 0.78]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)



G.3.5.3 Comparison of lamividine (no vaccine) versus no therapy (no vaccine)

Figure 686: HBsAg seropositivity at birth (newborns)

Study or Subgroup	Lamivudine Events	Lamivudine Total	No therapy Events	No therapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2012	1	43	8	52	100.0%	0.15 [0.02, 1.16]
Total (95% CI)		**43**		**52**	**100.0%**	**0.15 [0.02, 1.16]**
Total events	1		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)

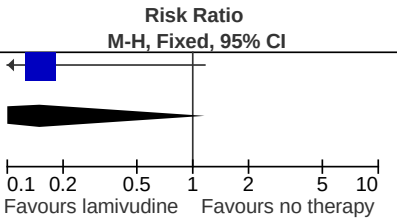


Figure 687: HBeAg seropositivity at birth (newborns)

Study or Subgroup	Lamivudine Events	Lamivudine Total	no therapy Events	no therapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yu 2012	7	43	11	52	100.0%	0.77 [0.33, 1.81]
Total (95% CI)		**43**		**52**	**100.0%**	**0.77 [0.33, 1.81]**
Total events	7		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

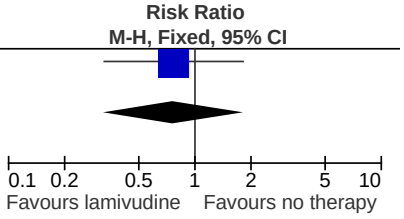


Figure 688: HBV DNA positivity at birth (newborns)

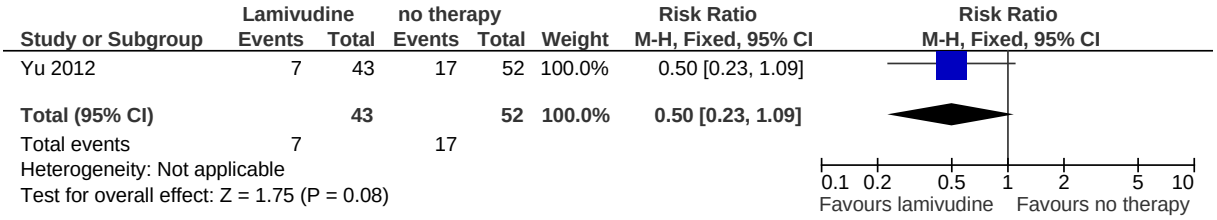
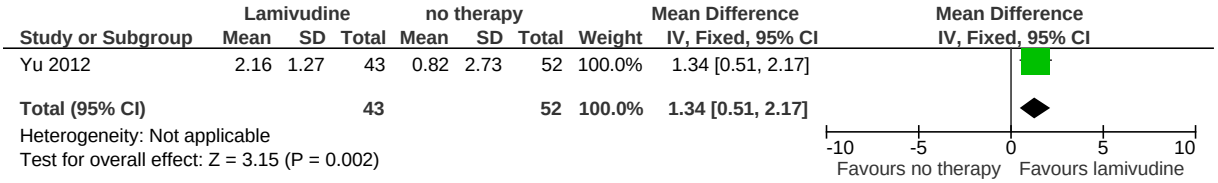


Figure 689: maternal HBV DNA reduction (after administration of agents)



G.3.5.4 Comparison of telbivudine (vaccine+ HBIG) versus no therapy (vaccine+ HBIG)

Figure 690: HBsAg positivity at birth (newborns)

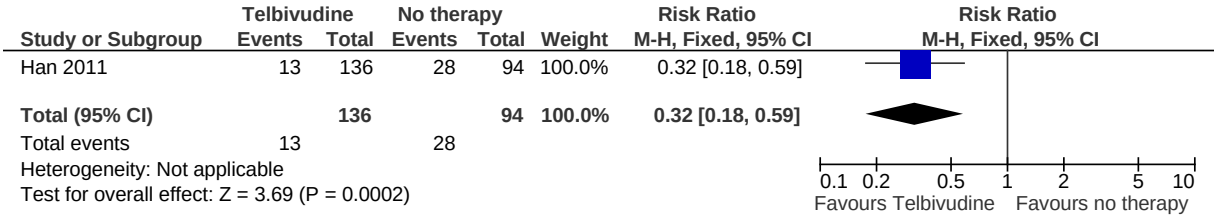


Figure 691: HBeAg positivity at birth (newborns)

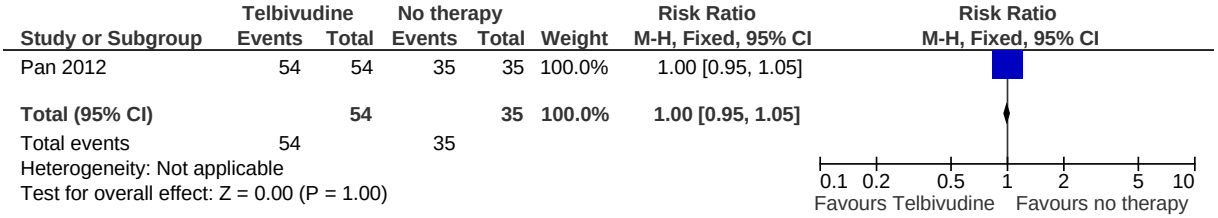


Figure 692: HBV DNA positivity at birth (newborns)

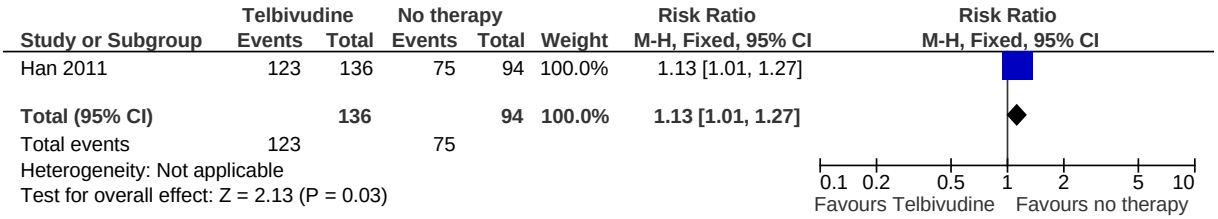


Figure 693: HBsAg positivity at week 28 (infants)

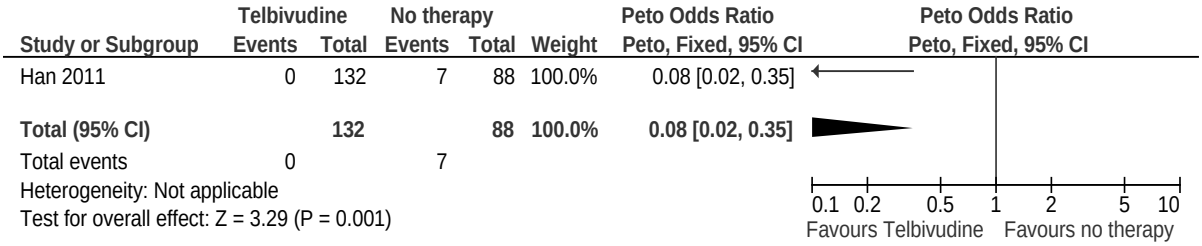


Figure 694: HBeAg positivity at week 28 (infants)

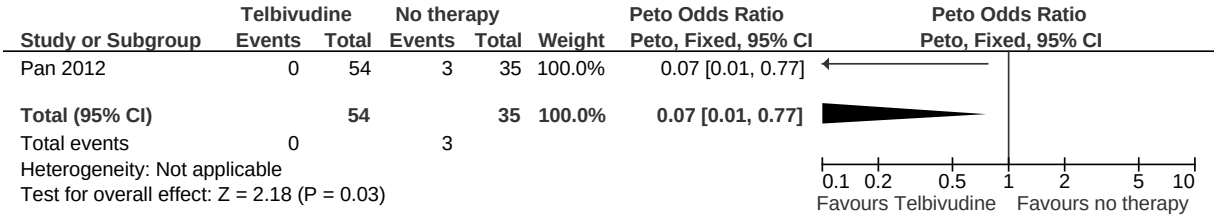


Figure 695: HBV DNA positivity at week 28 (infants)

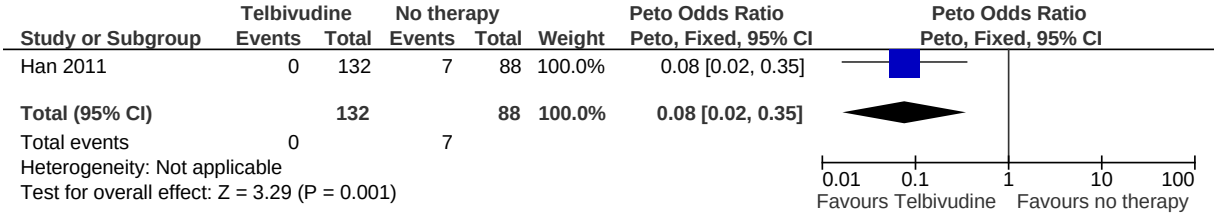


Figure 696: pneumonia (infants)

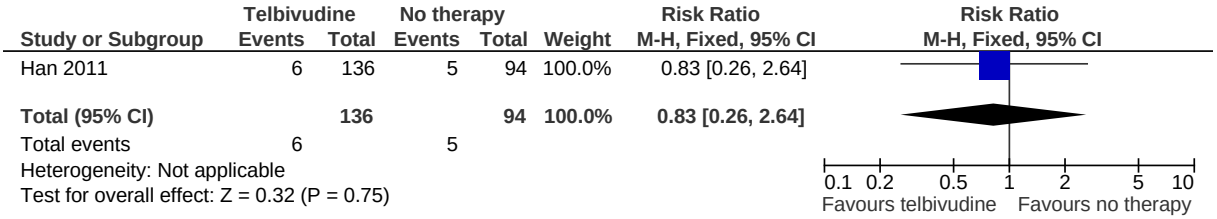


Figure 697: low birth weight

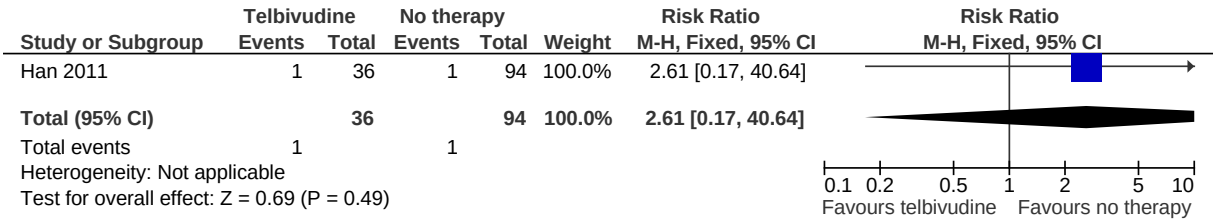


Figure 698: maternal undetectable HBV DNA (<500 copies/ml)

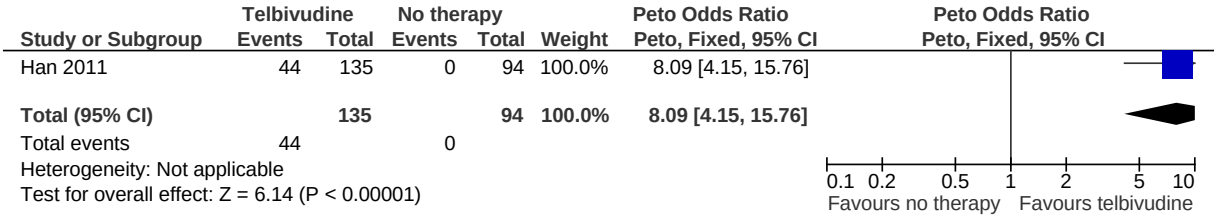


Figure 699: adverse events (mothers)

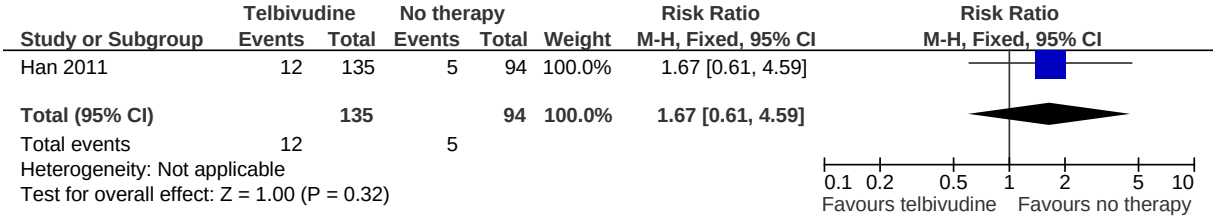
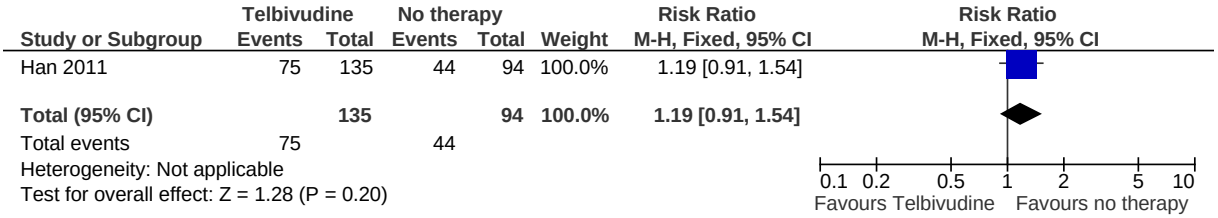
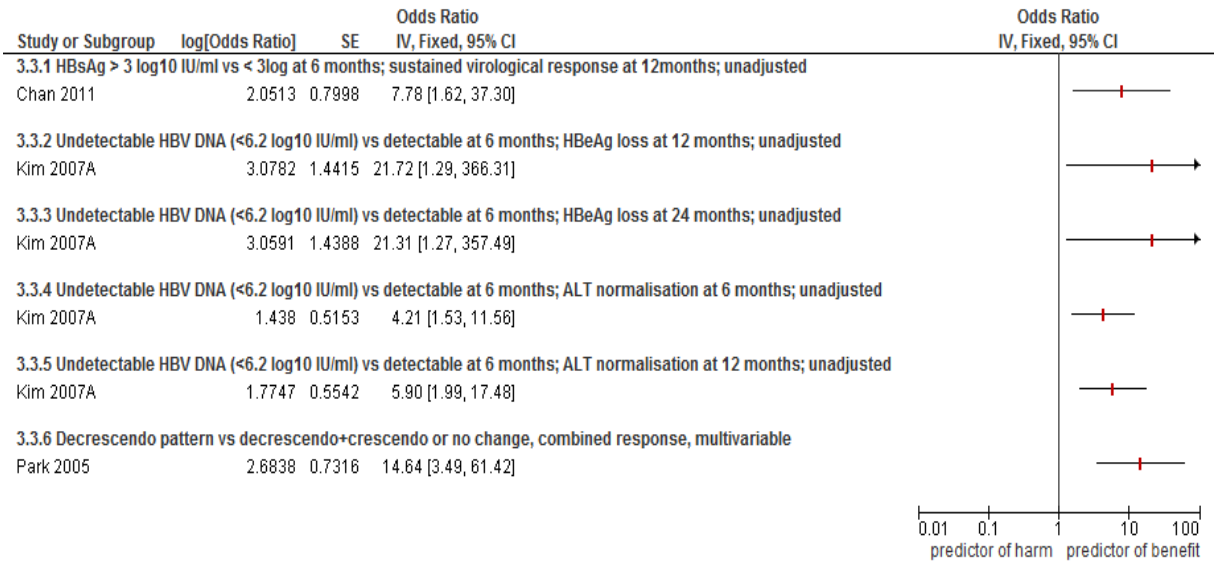


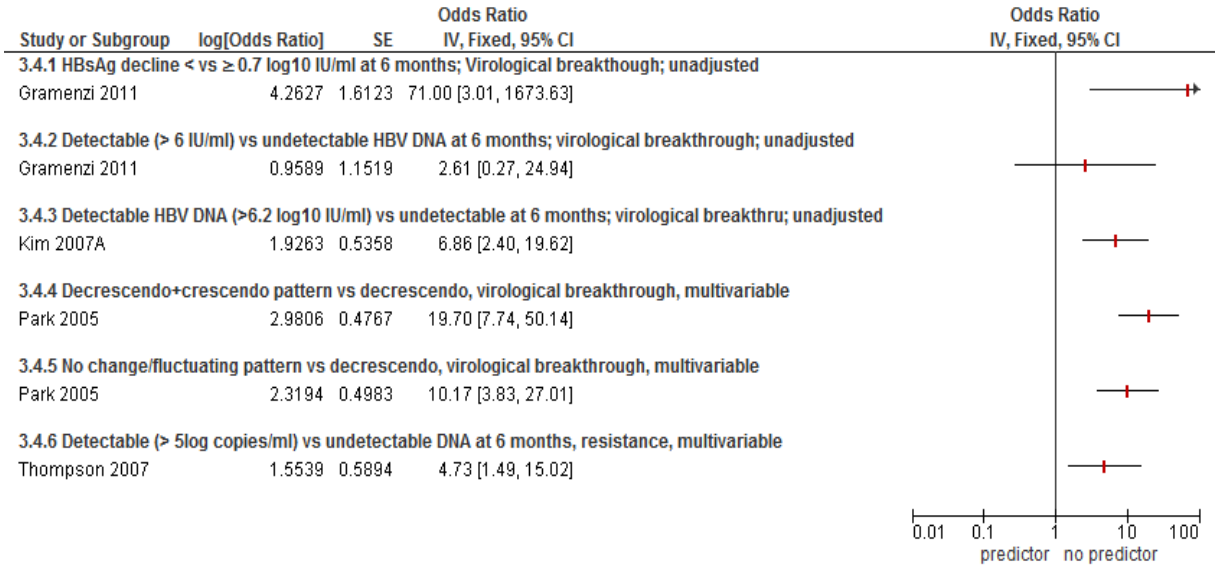
Figure 700: caesarean section



G.4 Monitoring

Figure 701: Patients with CHB on Lamivudine treatment





G.5 Surveillance

G.5.1 6 monthly vs. 12 monthly intervals of HCC surveillance

Figure 702: % patients with solitary hepatocellular carcinoma ≤3cm (retrospective studies)

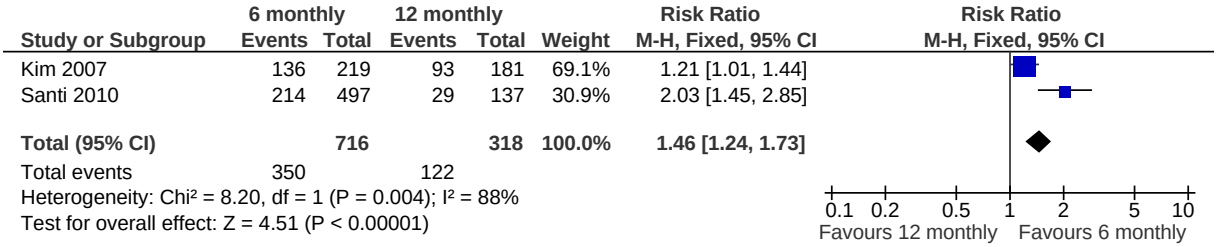


Figure 703: % patients with solitary hepatocellular carcinoma ≤3cm (sensitivity analysis including studies with at least 2/3 hepatitis B patients)

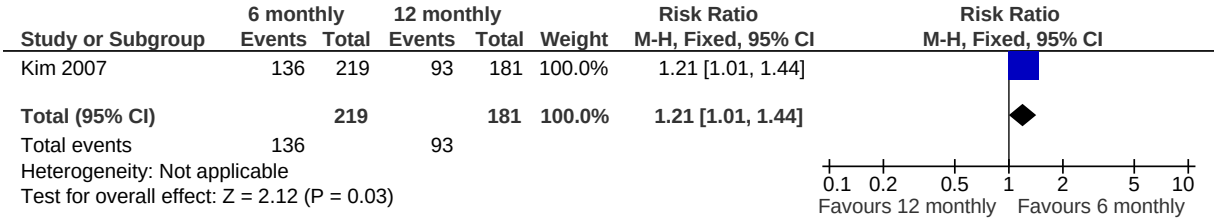
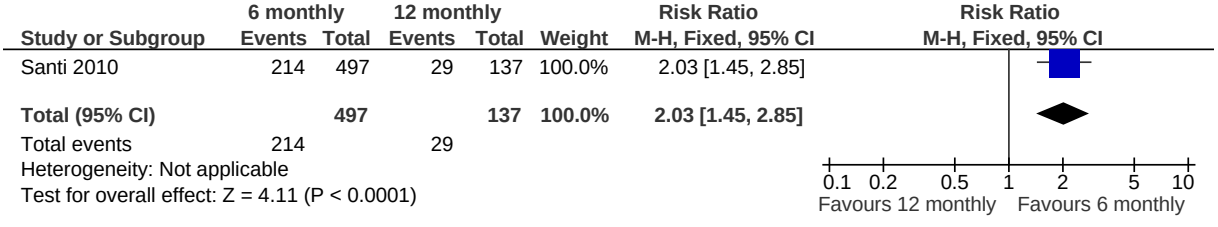


Figure 704: % patients with solitary hepatocellular carcinoma ≤3cm (sensitivity analysis including studies with a small proportion of hepatitis B patients)



G.5.2 6 monthly versus 3 monthly intervals of HCC surveillance

Figure 705: % patients with hepatocellular carcinoma (median of 47 months) (randomised study)

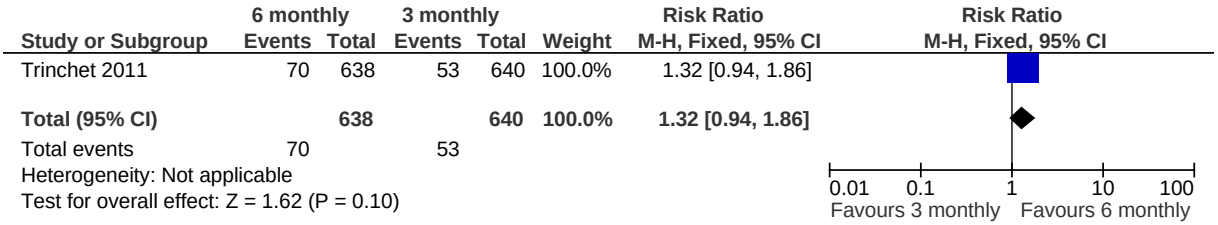


Figure 706: Mortality (median of 47 months) (randomised study)

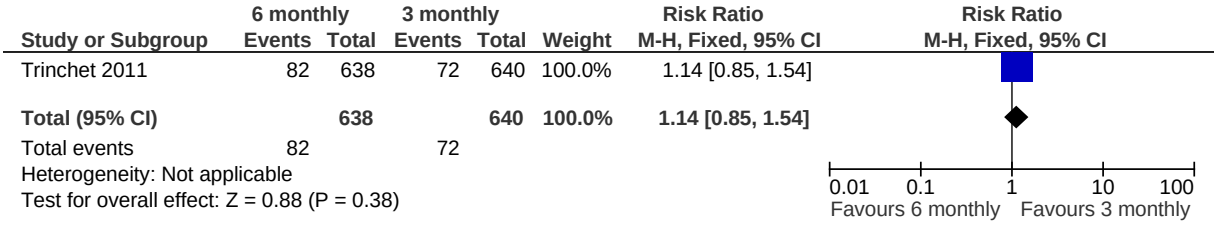


Figure 707: Mortality from liver failure (median of 47 months) (randomised study)

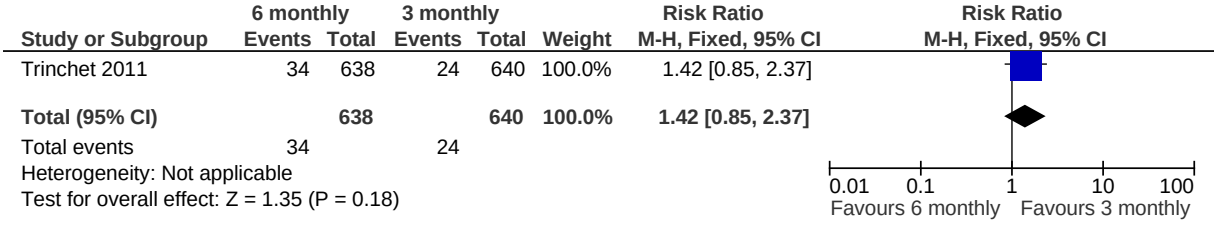
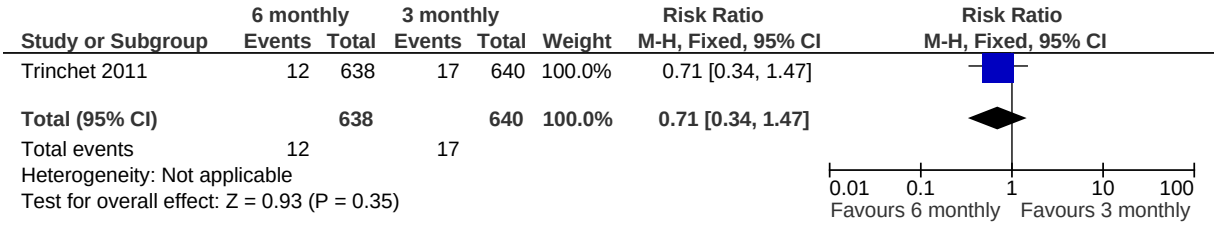


Figure 708: Mortality from hepatocellular carcinoma (median of 47 months) (randomised study)



G.5.3 4 monthly versus 12 monthly intervals of HCC surveillance

Figure 709: % patients with hepatocellular carcinoma (4 years follow up) (prospective study)