NICE advice

Pre-exposure prophylaxis of HIV in adults at high risk: Truvada (emtricitabine/tenofovir disoproxil)

Evidence summary
Published: 5 October 2016
nice.org.uk/guidance/esnm78

Key points from the evidence

The content of this evidence summary was up-to-date in October 2016. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

This evidence summary reviewed 4 randomised trials of Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for pre-exposure prophylaxis (PrEP) of HIV in either HIV-negative men or transgender women who have sex with men, or HIV-negative individuals in a heterosexual partnership with a person already infected with HIV. In these trials, Truvada reduced the relative risk of acquiring HIV infection by between 44% and 86% compared with placebo or no prophylaxis, which is equivalent to approximate numbers needed to treat of between 13 and 68 per year. In all trials, Truvada was given in addition to a comprehensive package of prevention services including HIV testing, risk-reduction counselling, condoms and sexually transmitted infection management. In addition to efficacy, issues relating to uptake, adherence, sexual behaviour, drug resistance, safety, prioritisation for prophylaxis and cost-effectiveness are also important to consider, especially at a population level.

Regulatory status: A licence extension for the use of once-daily Truvada for PrEP was approved by the European Medicines Agency in August 2016. The aim of this evidence summary is to inform forward planning around the use of Truvada for PrEP within local health systems.

Effectiveness	Safety
• In 3 randomised trials of PrEP in men or transgender women who have sex with men, Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) reduced the relative risk of acquiring HIV infection by the following amounts (modified intention to treat [mITT] populations): – 44% compared with placebo (iPrEx, n=2441; Truvada given daily; number needed to treat [NNT] 62 per year) – 86% compared with no prophylaxis (PROUD, n=523; Truvada given daily; NNT 13 per year) – 86% compared with placebo (IPERGAY, n=400; Truvada given 'on demand'; NNT 18 per year). • In 1 randomised trial of PrEP in serodiscordant heterosexual couples, once-daily Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) reduced the relative risk of acquiring HIV infection by 75% compared with placebo (Partners PrEP, n=3136, mITT population; NNT 68 per year).	• Emtricitabine and tenofovir are primarily excreted by the kidneys. The summary of product characteristics for Truvada has cautions about renal safety and monitoring, and states that it is not recommended for PrEP in people with creatinine clearance <60 ml/min. Cases of elevated creatinine levels were seen with Truvada in the 4 trials reviewed in this evidence summary. • The summary of product characteristics for Truvada has cautions about bone safety. Small decreases in bone mineral density were seen with Truvada in a sub-study of iPrEx. • Emtricitabine and tenofovir have shown activity against hepatitis B virus and stopping Truvada in people infected with hepatitis B virus may be associated with severe acute exacerbations. • A potential disadvantage of PrEP is the development and transmission of drug-resistant viruses. The risk of drug resistance seems low overall, and occurs mainly in people infected with HIV when PrEP is started, but monitoring at a population level is important. Truvada for PrEP is contraindicated in people with unknown or positive HIV-1 status, and the summary of product characteristics recommends reconfirming HIV-negative status at frequent intervals during use.

Patient factors	Resource implications
• The summary of product characteristics for Truvada states that people should be counselled to strictly adhere to the recommended dosing schedule. The effectiveness of Truvada for PrEP is strongly correlated with adherence as demonstrated by measurable drug levels in blood. Drug level monitoring in studies suggested varying levels of adherence. • The licence extension for Truvada for PrEP is for a dose of 1 tablet taken once daily. 'On demand' use of Truvada is not licensed for PrEP. • The summary of product characteristics lists the most frequently reported adverse reaction to Truvada for PrEP as headache (1%). • There have been concerns that sexual behaviour could become more high-risk if people are taking PrEP. However, providing PrEP may increase access to other health services such as HIV testing, sexually transmitted infection and hepatitis B screening, and support for high-risk sexual behaviour and recreational drug and alcohol use. Monitoring such data at a population level is important to assess the ongoing impact of PrEP.	• The NHS list price of Truvada is £355.73 for 30 tablets (MIMS, August 2016). However, it is currently purchased at a discounted net price for treating HIV.

Introduction and current guidance

The number of people living with HIV in the UK continues to increase and the number living with undiagnosed HIV remains high (Public Health England, situation report 2015). The HIV epidemic

remains largely concentrated among gay, bisexual and other men who have sex with men and among men and women of black African ethnicity. Despite a decline in undiagnosed HIV infections among men who have sex with men there is evidence that rates of ongoing HIV transmission remain high and the Public Health England report emphasises the need for high impact, appropriately tailored combination prevention strategies and programmes in this population. This includes early diagnosis of HIV infection through HIV testing, antiretroviral therapy for those diagnosed positive to reduce the risk of onward transmission, correct and consistent condom use, and addressing the wider determinants of poor sexual health in this population.

In June 2015, the use of antiretroviral therapy by people who are HIV positive to both prevent as well as treat HIV infection (treatment as prevention or TasP) was approved by NHS England (NHS England, Treatment as Prevention in HIV infected adults, 2015). At present there is no publicly funded pre-exposure prophylaxis (PrEP) programme in the UK. See the NHS England website for current information around the commissioning of PrEP.

This evidence summary considers the best available evidence for the efficacy and safety of Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for the licence extension for PrEP in the UK setting.

Full text of introduction and current guidance.

Product overview

Truvada is an antiretroviral drug licensed for combination therapy for treating HIV-1 infected adults aged 18 years and over. Each tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir). In August 2016, the European Medicines Agency (EMA) approved a licence extension for the use of Truvada for PrEP. The new indication is for the use of once-daily Truvada in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk (Truvada summary of product characteristics).

Full text of product overview.

Evidence review

The EMA submission for the licence extension for the use of Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for PrEP was based on that submitted to the US Food and Drug Administration (FDA) for the US licence (personal communication, Gilead, June 2016). The key

clinical studies therefore supporting the European application are the iPrEX study (Grant et al. 2010) and the Partners PrEP study (Baeten et al. 2012 and Baeten et al. 2014). The application also mentions the PROUD study (McCormack et al. 2016) and the IPERGAY study (Molina et al. 2015). See the European Public Assessment Report (EPAR) for more information.

This evidence summary focuses on these 4 randomised trials as they provide the best available evidence for the use of Truvada for PrEP in a UK setting. It also considers a World Health Organisation (WHO) systematic review and meta-analysis of oral PrEP for all populations (Fonner et al. 2015), which includes 9 other studies of Truvada for PrEP and 4 studies of tenofovir disoproxil alone for PrEP.

- The iPrEx study (Grant et al. 2010) was a double-blind RCT evaluating once-daily Truvada or placebo in 2499 HIV-negative men or transgender women who have sex with men with evidence of high-risk behaviour for HIV infection. In was conducted in Peru, Ecuador, Brazil, the US, Thailand and South Africa.
- The Partners PrEP study (Baeten et al. 2012 and Baeten et al. 2014) was a double-blind RCT evaluating once-daily single agent tenofovir disoproxil or Truvada or placebo in 4747 HIV-negative individuals in a heterosexual partnership with a person already infected with HIV (a serodiscordant heterosexual couple) in Kenya and Uganda.
- The PROUD study (McCormack et al. 2016) was an open-label trial of once-daily Truvada in 544 HIV-negative men or transgender women who have sex with men in England. Participants were randomised to start PrEP with Truvada immediately on study entry or after a deferral period.
- The IPERGAY study (Molina et al. 2015) was a double-blind RCT evaluating Truvada or placebo taken 'on demand' before and after sexual activity in 414 high-risk men who have sex with men in France and Canada.

Effect of emtricitabine and tenofovir disoproxil (Truvada) on HIV acquisition

In 3 of the 4 randomised trials reviewed in this evidence summary, Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) was evaluated for PrEP in HIV-negative men or transgender women who have sex with men (iPrEx, PROUD and IPERGAY). Men with high-risk sexual behaviour for HIV infection were recruited, and Truvada was given in addition to a comprehensive package of prevention services including HIV testing, risk-reduction counselling, condoms, and sexually transmitted infection management.

- In iPrEx (Grant et al. 2010, which had a median follow-up of 1.2 years), once-daily Truvada reduced the relative risk of acquiring HIV infection by 44% compared with placebo. In the Truvada group 36/1224 had emergent HIV infection and in the placebo group this was 64/1217 (hazard ratio [HR] 0.56; 95% confidence interval [CI] 0.37 to 0.85, p=0.005). However, efficacy was strongly correlated with adherence (see below). In a secondary analysis of this study (Buchbinder et al. 2014), the HIV incidence in the placebo group was calculated at 3.9 cases per 100 person-years, and the overall NNT was 62 per year (95% CI 44 to 147).

- In PROUD (McCormack et al. 2016, which had 243-person years of follow-up in the immediate PrEP group and 222-person years of follow-up in the deferred PrEP group) once-daily Truvada reduced the relative risk of acquiring HIV infection by 86% compared with no prophylaxis. There were 3/268 people with emergent HIV infection in the group randomised to Truvada immediately on study entry compared with 20/255 in the group where Truvada was deferred and people received no prophylaxis. This equated to a rate difference of 7.8 cases per 100 person-years (90% CI 4.3 to 11.3; 1.2 cases per 100 person-years in the immediate group compared with 9.0 cases per 100 person-years in the deferred group; relative risk reduction [RRR] 86%, 90% CI 64% to 96%; NNT 13 per year, 90% CI 9 to 23).

- In IPERGAY (Molina et al. 2015, which had a median follow-up of 9.3 months), Truvada was given 'on demand' before and after sexual activity rather than regularly once daily. Participants took a median of 15 tablets per month (interquartile range 11 to 21 in the Truvada group). 'On-demand' Truvada reduced the relative risk of acquiring HIV infection by 86% compared with placebo. In the Truvada group 2/199 had emergent HIV infection, a rate of 0.9 cases per 100 person-years, and in the placebo group this was 14/201, a rate of 6.6 cases per 100 person-years (RRR 86%; 95% CI 40% to 98%, p=0.002). This equates to a rate difference of 5.7 cases per 100 person-years or an NNT of 18 per year (95% CI 15 to 38).

The fourth randomised trial reviewed in this evidence summary (Partners PrEP; Baeten et al. 2012 and Baeten et al. 2014, which had an initial median follow-up of 23 months) evaluated Truvada for PrEP in HIV-negative individuals from serodiscordant heterosexual couples in Kenya and Uganda. It found once-daily Truvada reduced the relative risk of acquiring HIV infection by 75% compared with placebo. There were 13/1568 people with emergent HIV infection in the Truvada group, a rate of 0.50 cases per 100 person-years, compared with 52/1568 in the placebo group, a rate of 1.99 cases per 100 person-years (HR 0.25; 95% CI 0.13 to 0.45, p<0.001). This equates to a rate difference of 1.49 cases per 100 person-years or an NNT of 68 per year (95% CI 58 to 92).

Uptake and adherence

- In the iPrEx study, the 44% reduction in the relative risk of acquiring HIV infection was not as high as had been hypothesised and was less than that seen in other studies. Although the reported use of Truvada was high in this study (pill count suggested a median range of 89% to 95% use), drug level monitoring in a pre-specified subgroup found that exposure was substantially lower than this (emtricitabine or tenofovir was detected in only 9% of people with HIV infection and 51% of people who were HIV-negative).

- In the immediate Truvada group in the PROUD study, sufficient study drug was prescribed for 88% of the total follow up time, and tenofovir was detected in all 52 sampled participants who reported they were taking PrEP.

- In the IPERGAY study, participants took a median of 15 tablets per month in both the Truvada and placebo groups (interquartile range 11 to 21 in the Truvada group). However, individual patterns of tablet use showed large interpatient and intrapatient variability over time. The rates of detection for tenofovir diphosphate and emtricitabine were 86% and 82% respectively in participants in the active treatment group who had drug levels measured. However, based on computer-assisted structured interviews, although 43% of people took the assigned drug correctly during the most recent sexual intercourse, 29% took a suboptimal dose and 28% did not take the assigned drug at all.

Sexual practices

- In the iPrEx study, self-reported sexual practices were similar in the Truvada and placebo groups at all time points. However, one purpose of using placebo was to avoid confounding bias due to risk compensation (participants knew they might be taking an inactive treatment), and in both groups a comprehensive package of prevention services was given. The self-reported total number of sexual partners decreased and the percentage who used a condom increased in both groups after enrolment in the study. In the open-label follow-up of this study and others (Grant et al. 2014), the self-reported total number of sexual partners and non-condom anal intercourse decreased during follow-up in the group receiving PrEP and in the group not receiving PrEP. Syphilis incidence was also similar in both groups.

- In the PROUD study, where no placebo was given and people knew whether they were taking PrEP or not, questionnaires about sexual behaviour in the previous 90 days found that there was no difference between groups in the total number of sexual partners (p=0.57) at 1 year. However, more people in the immediate Truvada group reported receptive anal sex with 10 or more partners without a condom compared with the deferred group (21% compared with 12%, p=0.03). The frequency of bacterial sexually transmitted infections was not statistically

significantly different between groups when adjusted for the number of screens for infections (p=0.74). Antiretroviral post-exposure prophylaxis was prescribed to 12 people (14 courses) in the immediate Truvada group and 85 people (174 courses) in the deferred group.

- In the IPERGAY study, sexual practices did not change overall during the study period compared with baseline in either the active or placebo group.

HIV-drug-resistance

- In the iPrEx study, among 10 people who had HIV infection at enrolment, 3 people had an emtricitabine-resistant infection and none had a tenofovir-resistant infection. Among 100 people who became infected with HIV during the study (36 of whom were randomised to active treatment), no emtricitabine or tenofovir resistance was detected.
- In the Partners PrEP study, among 8 people in the tenofovir disoproxil alone or Truvada groups who were infected with HIV at baseline, 1 person had an emtricitabine-resistant infection and 1 person had a tenofovir-resistant infection. No participants who acquired HIV after randomisation were infected with a resistant HIV strain.
- In the PROUD study, 2 people in the immediate Truvada group who had HIV infection at baseline or at the 4-week visit developed an emtricitabine-resistant mutation. No resistance was detected in people who developed HIV at later time points and no participants developed a tenofovir-resistant mutation.
- In the IPERGAY study, none of the 16 people who developed HIV infection after enrolment had resistant mutations to tenofovir or emtricitabine.

Safety issues

- The safety data such as that contained in the summary of product characteristics (SPC) for Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) are largely derived from its use as treatment in people who are HIV positive. The risk of adverse effects when Truvada is used for PrEP is less well described, although some information is available in the SPC.
- The SPC for Truvada states that emtricitabine and tenofovir are primarily excreted by the kidneys, and renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy have been reported with the use of tenofovir disoproxil for treating HIV infection. The SPC recommends that creatinine clearance is calculated in all people before starting Truvada for either treatment or prevention and renal function should also be monitored during use. There are cautions around use in people with impaired renal function, and concurrent or recent use of a nephrotoxic medicine (including NSAIDs; see the SPC for

details). The SPC states that Truvada for PrEP has not been studied in people with creatinine clearance <60 ml/min and is therefore not recommended for use in this population.

- Elevated creatinine levels were seen in 2% of the Truvada group and 1% of the placebo group (p=0.08) in the iPrEx study, but all resolved after the study drug was stopped. Elevated creatinine levels were also seen in 18% of the Truvada group and 10% of the placebo group (p=0.03) in the IPERGAY study, but none led to discontinuation of the study drug. In PROUD, 3/275 people in the immediate Truvada group interrupted treatment because of high creatinine levels, but the study drug was restarted in all these people.

- The SPC states that small decreases in bone mineral density of the hip and spine were seen in a study of treatment with tenofovir disoproxil in people who were antiretroviral-naive, but there was no increased risk of fractures or evidence for clinically relevant bone abnormalities.

- In a sub-study of iPrEx (Mulligan et al. 2015), a statistically significant decrease in bone mineral density of −0.91% in the spine (p=0.001) and −0.61% in the hip (p=0.001) was seen with Truvada compared with placebo by 24 weeks. Among all people in the main iPrEx study there were fractures in 1.7% of the Truvada group and 1.4% of the placebo group (p=0.62).

- The SPC states that people with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. The safety and efficacy of Truvada for PrEP in people with hepatitis B or C has not been established. Emtricitabine and tenofovir individually and in combination have shown activity against hepatitis B virus in pharmacodynamic studies, and discontinuation of Truvada in people infected with hepatitis B virus may be associated with severe acute exacerbations of hepatitis.

- The SPC states that the most frequently reported adverse reactions considered possibly or probably related to treatment with emtricitabine or tenofovir disoproxil fumarate are nausea (12%) and diarrhoea (7%). It also states that no new adverse reactions were identified from the iPrEx and Partners PrEP studies, and the most frequent adverse reaction reported in the Truvada group in the iPrEx study was headache (1%). In iPrEx and IPERGAY there were increased rates of gastrointestinal events with Truvada compared with placebo. In the Partners PrEP study, there were increased reports of gastrointestinal side effects and fatigue in the Truvada group, mainly during the first month. In PROUD, 21/275 (8%) people in the immediate Truvada group interrupted or missed doses because of adverse events (most commonly nausea, headache and arthralgia), but study drug was restarted in 20 of these people.

Evidence strengths and limitations

- Of the 4 randomised trials reviewed in this evidence summary, 3 evaluated Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for PrEP in HIV-negative men or transgender women who have sex with men. These were the iPrEx study conducted in Peru, Ecuador, Brazil, US, Thailand and South Africa; the PROUD study conducted in England; and the IPERGAY study conducted in France and Canada.
- The PROUD study is directly relevant to the use of Truvada for PrEP in the UK but its design has strengths and limitations. Its open-label, real-world design represents how PrEP would be used in routine clinical practice, but it increases the risk of bias because both participants and clinicians knew the allocation of study treatment. The incidence of HIV infection was high in the control group in this study, and this was the main determinant of the NNT of 13, which was lower than in other studies.
- The IPERGAY study assessed 'on demand' use of Truvada before and after sexual activity rather than regular once-daily use as in the UK licence extension for PrEP. Participants in IPERGAY took a median of 15 tablets per month, but individual patterns of tablet use showed large interpatient and intrapatient variability over time.
- The fourth randomised trial (Partners PrEP) evaluated Truvada for PrEP in HIV-negative heterosexual men and women. This RCT was conducted in Africa and the findings may be less relevant to a UK population.
- Other trials of Truvada in heterosexual men and women have been published, but these were largely conducted in Africa (for example VOICE, TDF2 and FEM-PrEP).
- The WHO systematic review included 1 study of PrEP in people who inject drugs (the Bangkok tenofovir study). However, this was with tenofovir disoproxil only and was conducted in drug-treatment clinics in Thailand, which are not representative of the population of people who inject drugs in the UK.

Full text of evidence review.

Context

Prevention strategies for HIV include early diagnosis of HIV infection through HIV testing, antiretroviral therapy for those diagnosed positive to reduce onward transmission (treatment as prevention [TasP]), correct and consistent condom use, and addressing the wider determinants of

high-risk sexual behaviour. Using antiretroviral agents to prevent HIV acquisition in those who are HIV negative (PrEP) is also an option (Public Health England, situation report 2015).

In the European AIDS Clinical Society (EACS) guidelines from 2015 the recommended PrEP regimen is 1 tablet of emtricitabine/tenofovir disoproxil 200 mg/245 mg once daily. For men who have sex with men with high-risk sexual behaviour, these guidelines recommend that 'on demand' emtricitabine/tenofovir disoproxil 200 mg/245 mg may be given. WHO guidelines from 2016 recommend oral PrEP containing tenofovir disoproxil (no particular regimen is recommended).

The cost of Truvada is £355.73 for 30 tablets (MIMS, August 2016). However, it is currently purchased for treating HIV at discounted net price through the Commercial Medicines Unit (CMU) regional framework (personal communication, Gilead, June 2016). Costs of Truvada given 'on demand' (based on an average use of 15 tablets per month) or as separate tenofovir disoproxil 245 mg (Viread) and emtricitabine 200 mg (Emtriva) tablets are given in the full evidence summary. However, Truvada is the only antiretroviral product licensed for use as PrEP in the UK. The licence extension is for once-daily use: 'on demand' use of Truvada, tenofovir disoproxil (Viread) alone, or with emtricitabine (Emtriva) as separate tablets, is not licensed for PrEP.

Full text of context.

Estimated impact for the NHS

Likely place in therapy

At present there is no publicly funded PrEP programme in the UK. See the NHS England website for current information around the commissioning of PrEP.

European AIDS Clinical Society (EACS) guidelines from 2015 and WHO guidelines from 2016 both recommend PrEP for people at high-risk of acquiring HIV infection. The European guidelines recommend PrEP for HIV-negative men who have sex with men and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not on treatment. These guidelines also state that PrEP may be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and are likely to have HIV-positive partners who are not on treatment. The WHO guidelines recommend PrEP as an additional prevention choice for people at 'substantial risk' of HIV infection (populations with a HIV incidence of around 3 cases per 100 person-years or higher), such as men who have sex with men, transgender women, and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection.

In May 2016, BHIVA and BASHH published a position statement on PrEP in the UK, which recommends that PrEP be made available within a comprehensive HIV prevention package to:

- men who have sex with men, trans men and trans women who are engaging in condomless anal sex
- HIV-negative partners who are in serodiscordant heterosexual and same-sex relationships with a HIV-positive partner whose viral replication is not supressed
- other heterosexuals considered to be at high risk.

Evidence for the use of Truvada for PrEP that is most relevant to the UK population relates to its use by men who have sex with men. This group in particular has ongoing high rates of HIV transmission and acquisition, and the Public Health England situation report on HIV emphasises the need for high impact, appropriately tailored combination prevention strategies and programmes for this group. Both the Public Health England report and the BHIVA-BASHH position statement stress that PrEP is only one of several prevention tools for HIV, and early diagnosis through testing, antiretroviral therapy for people who are HIV-positive to reduce the risk of onward transmission, correct and consistent condom use, and addressing the wider determinants of poor sexual health among this population are also important.

There is little doubt that Truvada is effective in reducing HIV acquisition in high-risk people who are HIV-negative. However, issues relating to uptake, adherence, sexual behaviour, drug resistance, safety, prioritisation for prophylaxis and cost-effectiveness are also important to consider, especially at a population level.

Full text of estimated impact for the NHS.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

The number of people living with HIV in the UK continues to increase and the number living with undiagnosed HIV remains high (Public Health England, situation report 2015). In 2014, an estimated 103,700 people were living with HIV in the UK (69,200 men and 34,400 women) and an estimated 18,100 (17%) of them were unaware of their infection and at risk of unknowingly passing on HIV if having sex without a condom. The HIV epidemic remains largely concentrated among gay, bisexual and other men who have sex with men and among men and women of black African ethnicity. Despite a decline in undiagnosed HIV infections among men who have sex with men there is evidence that rates of ongoing HIV transmission remain high. An estimated 45,000 men living with HIV in the UK in 2014 had acquired their infection through sex with other men, an increase from 43,000 in 2013. Among men and women who acquired HIV through heterosexual sex, 55% of men (9,900/21,300) and 62% of women (20,100/32,700) were of black African ethnicity in the UK in 2014. An estimated 2160 people who inject drugs were living with HIV in the UK in 2014.

The Public Health England report states that the ongoing high rates of HIV transmission and acquisition among men who have sex with men in particular emphasises the need for high impact, appropriately tailored combination prevention strategies and programmes. This includes early diagnosis of HIV infection through HIV testing, antiretroviral therapy for those diagnosed positive to reduce the risk of onward transmission, correct and consistent condom use, and addressing the wider determinants of poor sexual health among this population which are closely linked to HIV infection, such as reducing the number of sexual partners and avoiding overlapping sexual relationships.

The report also states that the evidence for the efficacy and effectiveness of antiretroviral agents to reduce onward transmission from people who are HIV positive and to prevent HIV acquisition in those who are HIV negative continues to expand, making important additions to the prevention toolkit.

People living with HIV who are on effective antiretroviral therapy are very unlikely to pass on HIV to sexual partners. In June 2015, the use of antiretroviral therapy by people who are HIV positive to both prevent as well as treat HIV infection (treatment as prevention or TasP) was approved by NHS England (NHS England, Treatment as Prevention in HIV infected adults, 2015). There is also a NICE accredited UK national guideline for the use of HIV post-exposure prophylaxis following sexual exposure (PEPSE). However, at present there is no publicly funded pre-exposure prophylaxis

(PrEP) programme in the UK. See the NHS England website for current information around the commissioning of PrEP.

The European AIDS Clinical Society (EACS) guidelines from 2015 recommend that PrEP can be used in adults at high-risk of acquiring HIV infection. PrEP is recommended in HIV-negative men who have sex with men and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not on treatment. A recent sexually transmitted infection or use of post-exposure prophylaxis may be markers of increased risk for HIV acquisition. PrEP may also be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and likely to have HIV-positive partners who are not on treatment. The guidelines recommend that PrEP should be used in combination with other preventive interventions, including the use of condoms, and should be supervised by a doctor experienced with sexual health and use of HIV medicines, possibly as part of a shared-care arrangement.

The guidelines have specific recommendations around HIV testing, documenting hepatitis B virus serology status and screening for sexually transmitted infections. It also states that people should be counselled about renal and bone health, and the importance of adherence. The EACS guidelines recommend that PrEP can be prescribed long term but that each consecutive prescription should be for a maximum period of 3 months to ensure appropriate monitoring. The recommended PrEP regimen is 1 tablet of emtricitabine/tenofovir disoproxil 200 mg/245 mg once daily. For men who have sex with men with high-risk sexual behaviour the guidelines recommend that emtricitabine/tenofovir disoproxil may be given 'on demand' (with a double dose 2–24 hours before each sexual intercourse, followed by 2 single doses, 24 and 48 hours after the first drug intake). If dosed 'on demand', the total dose per week should not exceed 7 tablets.

WHO guidelines from 2016 recommend that oral PrEP containing tenofovir disoproxil should be offered as an additional prevention choice for people at 'substantial risk' of HIV infection as part of combination HIV prevention approaches. No particular regimen is recommended. 'Substantial risk' is provisionally defined as an HIV incidence of around 3 cases per 100 person-years or higher in the absence of PrEP. HIV incidence higher than 3 cases per 100 person-years has been identified among some groups of men who have sex with men, transgender women in many settings, and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection. Individual risk varies within groups at substantial risk, depending on individual behaviour and the characteristics of sexual partners.

This evidence summary considers the best available evidence for the efficacy and safety of Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for the licence extension for PrEP (use of

Truvada in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk) in the UK setting.

Product overview

Drug action

Truvada is an antiretroviral medicine for treatment and prophylaxis of HIV infection. Each tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir). Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil, which is converted in vivo to tenofovir, is a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to HIV-1, HIV-2 and hepatitis B virus. Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination (Truvada summary of product characteristics [SPC]).

Licensed therapeutic indication

Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) is licensed for antiretroviral combination therapy for treating HIV-1 infected adults aged 18 years and over. In August 2016, the European Medicines Agency (EMA) approved a licence extension for the use of Truvada for pre-exposure prophylaxis (PrEP). Truvada is licensed in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk (Truvada SPC). Truvada was licensed in the US for PrEP in 2012.

Course and cost

The recommended dose of Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for treating or preventing HIV in adults is 1 tablet, taken orally, once daily (Truvada SPC). The SPC states that to optimise the absorption of tenofovir, it is recommended that Truvada is taken with food.

The use of Truvada for PrEP is contraindicated in people with unknown or positive HIV-1 status. The SPC states that Truvada is not always effective in preventing the acquisition of HIV, and the time to onset of protection after starting Truvada is unknown. Truvada should only be used for PrEP as part of an overall HIV prevention strategy including consistent and correct condom use, knowledge of HIV status and regular testing for other sexually transmitted infections. Truvada

should only be used for PrEP in people who have been confirmed to be HIV negative, and this should be reconfirmed at frequent intervals (for example, at least every 3 months) using a combined antigen/antibody test. Truvada alone does not constitute a complete regimen for treating HIV, and resistant mutations have emerged in people with undetected HIV infection who are only taking Truvada. If clinical symptoms consistent with acute viral infection are present, and recent (<1 month) exposures to HIV are suspected, use of Truvada for PrEP should be delayed for at least 1 month and HIV status reconfirmed before starting Truvada (Truvada SPC).

The SPC states that the effectiveness of Truvada in reducing the risk of acquiring HIV is strongly correlated with adherence as demonstrated by measurable drug levels in blood, and people taking Truvada for PrEP should be counselled to strictly adhere to the recommended dosing schedule.

The cost of Truvada is £355.73 for 30 tablets (MIMS, August 2016). However, for treating HIV it is currently purchased at discounted net price through the Commercial Medicines Unit (CMU) regional framework (personal communication, Gilead, June 2016).

Evidence review

The EMA submission for the licence extension for Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for PrEP was based on that submitted to the US Food and Drug Administration (FDA) for the US licence (personal communication, Gilead, June 2016). The key clinical studies therefore supporting the European application are the iPrEx study (Grant et al. 2010) and the Partners PrEP study (Baeten et al. 2012 and Baeten et al. 2014). The application also mentions the PROUD study (McCormack et al. 2016) and the IPERGAY study (Molina et al. 2015). See the European Public Assessment Report (EPAR) for more information. This evidence summary reviews these 4 randomised trials as the 'best available evidence' for the use of Truvada for PrEP in the UK setting.

The iPrEx study (Grant et al. 2010) was a randomised controlled trial (RCT) evaluating once-daily Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) or placebo in 2499 HIV-negative men or transgender women who have sex with men with evidence of high-risk behaviour for HIV infection. In was conducted in Peru, Ecuador, Brazil, the US, Thailand and South Africa.

The Partners PrEP study (Baeten et al. 2012 and Baeten et al. 2014) was a RCT evaluating once-daily single agent tenofovir disoproxil or Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) or placebo in 4747 HIV-negative individuals in a heterosexual partnership with a person already infected with HIV (a serodiscordant heterosexual couple) in Kenya and Uganda.

The PROUD study (McCormack et al. 2016) was an open-label randomised trial of once-daily Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) started either immediately after randomisation or after a deferral period planned for 1 year in 544 HIV-negative men or transgender women who have sex with men in England.

The IPERGAY study (Molina et al. 2015) was a double-blind RCT evaluating Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) or placebo taken 'on demand' before and after sexual activity in 414 high-risk men who have sex with men in France and Canada.

A World Health Organisation (WHO) systematic review and meta-analysis of oral PrEP for all populations (Fonner et al. 2015) that was published alongside the 2016 WHO guidelines includes a further 9 studies of Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for PrEP in addition to the 4 studies reviewed in this evidence summary. These are:

- ADAPT study (HPTN 067; ClinicalTrials.gov Identifier: NCT01327651)
    - A randomised, 3-arm, open-label trial evaluating Truvada once daily; or twice per week and after sexual intercourse; or only before and after sexual intercourse, in 540 HIV-negative men who have sex with men, transgender women and heterosexual women in Thailand, the US and South Africa.
- FEM-PrEP (Van Damme et al. 2012)
    - A randomised, placebo-controlled trial evaluating once-daily Truvada or placebo in 2120 HIV-negative women in Kenya, South Africa and Tanzania.
- Grant et al. 2014
    - A 72-week open-label extension study of 1603 HIV-negative men and transgender women who have sex with men previously enrolled in ATN 082, the iPrEx study and the US Safety Study. In ATN 082 and the iPrEx study, people received PrEP with once-daily Truvada. In the US Safety Study, PrEP was with tenofovir disoproxil only.
- IAVI Kenya (Mutua et al. 2012)
    - A randomised, placebo-controlled trial evaluating once-daily or intermittent Truvada in 67 HIV-negative men who have sex with men and 5 HIV-negative female sex workers in Kenya.
- IAVI Uganda (Kibengo et al. 2013)

  - A randomised, placebo-controlled trial evaluating once-daily or intermittent Truvada in 72 HIV-negative individuals from serodiscordant heterosexual couples in Uganda.

- Partners PrEP Demonstration Project (ClinicalTrials.gov Identifier: NCT02775929)

  - An ongoing, open-label, prospective cohort study which enrolled 1013 high-risk, serodiscordant couples in Africa to determine barriers and facilitators to uptake and sustained adherence to daily oral PrEP with Truvada in HIV-negative partners.

- Project PREPARE (ATN 082; Hosek et al. 2013)

  - A randomised controlled 3-arm trial evaluating a behavioural HIV-prevention intervention alone, combined with once-daily Truvada or combined with placebo in 58 HIV-negative young men who have sex with men in the US.

- TDF2 (Thigpen et al. 2012)

  - A randomised, placebo-controlled trial evaluating once-daily Truvada or placebo in 1219 HIV-negative heterosexual men and women in Botswana.

- VOICE (Marrazzo et al. 2015)

  - A randomised, placebo-controlled trial evaluating once-daily Truvada, oral tenofovir disoproxil only, tenofovir vaginal gel or placebo in 5029 HIV-negative women in South Africa, Uganda and Zimbabwe.

The WHO systematic review and meta-analysis also includes 4 studies of tenofovir disoproxil alone for PrEP. These are the Bangkok tenofovir study (Choopanya et al. 2013) and its open-label extension (in people who inject drugs), the West African safety study (Peterson et al. 2007; in high-risk women in Africa) and the US safety study (Grohskopf et al. 2013; a US study in men who have sex with men). There are also many additional PrEP demonstration projects underway, which are discussed in a review article by Wilton et al. 2015. Many of these demonstration projects are in the US, with others in Canada and Australia.

iPrEx study (Grant et al. 2010)

- Design: phase 3, randomised, double-blind, placebo-controlled trial conducted in Peru, Ecuador, Brazil, the US, Thailand and South Africa.

- Population: HIV-negative men or transgender women (male sex at birth) aged 18 years or older who have sex with men and have evidence of high-risk behaviour for HIV infection. This includes no condom use during anal intercourse with a male HIV-positive partner or a male

partner of unknown HIV status during the last 6 months; anal intercourse with more than 3 male sex partners during the last 6 months; exchange of money, gifts, shelter, or drugs for anal sex with a male partner during the last 6 months; sex with a male partner and sexually transmitted infection diagnosis during the last 6 months or at screening; or sexual partner of an HIV-infected man with whom condoms are not consistently used in the last 6 months. In total, 4905 people were screened for inclusion in the trial and 2499 were randomised (the method of allocation concealment is unclear). The mean age in the Truvada group was 27.5 years and it was 26.8 years in the placebo group (p=0.04).

- Intervention and comparator: 1251 people were randomised to receive Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) once daily and 1248 people to placebo. This was in addition to a comprehensive package of prevention services including HIV testing, risk-reduction counselling, condoms, and diagnosis and treatment of symptomatic sexually transmitted infection. Vaccination against hepatitis B was also offered to all susceptible people (accepted by 94%). Study visits were every 4 weeks and these included drug dispensing, pill count, adherence counselling, HIV testing and taking medical history. Chemical and haematological analyses were performed at weeks 4, 8, 12, 16 and 24, and every 12 weeks after that. Follow-up was for a median of 1.2 years and a maximum of 2.8 years.

- Outcomes: the primary objectives were to determine if daily oral Truvada reduces HIV seroincidence compared with placebo, and if it was associated with comparable rates of adverse events to placebo. Therefore the primary end points were the incidence of documented HIV seroconversion defined by the follow-up HIV testing algorithm, and adverse events (grade 1 or higher creatinine toxicity confirmed by repeat testing; grade 3 or higher phosphorus toxicity confirmed by repeat testing; grade 2, 3, or 4 laboratory adverse events other than creatinine or phosphorus; grade 2, 3, or 4 clinical adverse events or HIV seroconversion). Secondary end points included hepatic transaminitis elevations among those with detectable hepatitis B; changes in bone mineral density, fat distribution, fasting lipids; HIV-drug-resistance among seroconverters, reported risk behaviour, sexually transmitted infection prevalence, pill counts and reported adherence.

Table 1 Summary of iPrEx study (Grant et al. 2010)

	Emtricitabine/tenofovir disoproxil 200 mg/245 mg (Truvada)	Placebo	Analysis
Randomised	n=1251	n=1248	

Efficacy (modified ITT population; emergent HIV infection)	n=1224 (25 people randomised had no HIV test after enrolment, 2 were infected at enrolment)	n=1217 (23 people randomised had no HIV test after enrolment, 8 were infected at enrolment)	
Primary outcome: incidence of documented HIV seroconversion	36 people had emergent HIV infection	64 people had emergent HIV infection	HR 0.56 (95% CI 0.37 to 0.85, p=0.005) RRR 44% (95% CI 15% to 63%)
Safety	n=1251	n=1248	
People reporting any adverse event	69% (867/1251)	70% (877/2611)	p=0.50
People reporting any serious adverse event	5% (60/1251)	5% (877/1248)	p=0.57
People with elevated creatinine level	2% (25/1251)	1% (14/1248)	p=0.08
People with nausea	2% (20/1251)	0.7% (9/1248)	p=0.04
People with unintentional weight loss (≥5%)	2% (27/1251)	1% (14/1248)	p=0.04
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; p, p value; RRR, relative risk reduction			

Partners PrEP study (Baeten et al. 2012 and Baeten et al. 2014)

- Design: phase 3, randomised, double-blind, placebo-controlled trial conducted in Kenya and Uganda.

- Population: HIV uninfected men and women in heterosexual HIV serodiscordant couples aged between 18 and 65 years old. Eligible couples were sexually active and intending to remain together as a couple. HIV seronegative partners had normal renal function, did not have hepatitis B and women were not pregnant or breastfeeding. HIV seropositive partners were not receiving antiretroviral therapy. Couples were not excluded from the study if either partner within the couple had other sexual partners; about 8% of seronegative partners reported sex with a third party (HIV status not stated). In total, 7856 couples were screened for inclusion in the trial and 4758 were randomised (the method of allocation suggests allocation was concealed). For 62% of the couples followed, the HIV seronegative partner was male. The median age was 33 or 34 years across groups.

- Intervention and comparator: 1589 people were randomised to receive tenofovir disoproxil 245 mg alone once daily, 1583 people to Truvada (emtricitabine/tenofovir disoproxil 200 mg/ 245 mg) once daily and 1586 people to placebo. This was in addition to a comprehensive package of prevention services including HIV testing, risk-reduction counselling, condoms, sexually transmitted infection management, referral for male circumcision and post-exposure prophylaxis. Vaccination against hepatitis B was also offered. Study visits were every month and these included drug dispensing, collection of unused medication, adherence counselling, HIV testing and assessment of sexual behaviour. Chemical and haematological analyses were performed at 1 month and quarterly thereafter. Follow-up was for a median of 23 months (range 1 to 36 months). After an interim review by an independent data and safety monitoring board, the placebo group was discontinued and participants initially randomised to this group were re-randomised to either of the active groups. A total of 1264 people from the placebo group were re-randomised to tenofovir disoproxil alone once daily (n=631) or Truvada (n=633).

- Outcomes: the primary objectives were to determine if once-daily tenofovir disoproxil or once-daily emtricitabine and tenofovir disoproxil (Truvada) reduces HIV acquisition compared with placebo, and to assess the safety of these regimens compared with placebo. The primary end points were therefore seropositivity in people previously seronegative for HIV and adverse events. Secondary objectives included an assessment of adherence, risk compensation (change in sexual behaviour), safety of chemoprophylaxis in women who become pregnant during the study and the frequency of antiviral resistance in people who acquired HIV.

Table 2 Summary of Partners PrEP study (Baeten et al. 2012 and Baeten et al. 2014)

	Tenofovir disoproxil 245 mg	Emtricitabine/ tenofovir disoproxil 200 mg/245 mg (Truvada)	Placebo	Analysis
Randomised	n=1589	n=1583	n=1586	
Efficacy (initial randomisation) (modified ITT population; emergent HIV infection)	n=1572 (5 people randomised were found to be ineligible after randomisation, a further 5 were infected at enrolment and 7 were lost to follow-up)	n=1568 (4 people randomised were found to be ineligible after randomisation, a further 3 were infected at enrolment and 8 were lost to follow-up)	n=1568 (2 people randomised were found to be ineligible after randomisation, a further 6 were infected at enrolment and 10 were lost to follow-up)	

Primary outcome: incidence of documented HIV seroconversion	17 people had emergent HIV infection 0.65 cases per 100 person-years	13 people had emergent HIV infection 0.50 cases per 100 person-years	52 people had emergent HIV infection 1.99 cases per 100 person-years	Tenofovir disoproxil vs. placebo HR 0.33 (95% CI 0.19 to 0.56, p<0.001) RRR 67% (95% CI 44% to 81%) Truvada vs. placebo HR 0.25 (95% CI 0.13 to 0.45, p<0.001) RRR 75% (95% CI 55% to 87%) Truvada vs. tenofovir disoproxil Not significantly different (p=0.23)
Efficacy (re-randomisation) (modified ITT population; emergent HIV infection)	n=2207 (8 people randomised were infected at enrolment)	n=2208 (4 people randomised were infected at enrolment)		

Primary outcome: incidence of documented HIV seroconversion	31 people had emergent HIV infection 0.71 cases per 100 person-years	21 people had emergent HIV infection 0.48 cases per 100 person-years		Truvada vs. tenofovir disoproxil HR 0.67 (95% CI 0.39 to 1.17, p=0.16)
Safety (initial randomisation)	n=1584	n=1579	n=1584	
People reporting any adverse event	85% (1350/1584)	86% (1362/1579)	85% (1350/1584)	Tenofovir disoproxil vs. placebo p=1.00 Truvada vs. placebo p=0.42
People reporting any serious adverse event	7% (118/1584)	7% (115/1579)	7% (118/1584)	Tenofovir disoproxil vs. placebo p=1.00 Truvada vs. placebo p=0.89
People with neutropenia	15% (238/1584)	18% (281/1579)	13% (209/1584)	Tenofovir disoproxil vs. placebo p=0.15 Truvada vs. placebo P<0.001
Safety (re-randomisation)	n=2215	n=2212		

People reporting any adverse event	91% (2010/2215)	91% (2016/2212)		Truvada vs. tenofovir disoproxil p=0.68
People reporting any serious adverse event	9% (209/2215)	9% (207/2212)		Truvada vs. tenofovir disoproxil p=0.96
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; p, p value; RRR, relative risk reduction				

PROUD study (McCormack et al. 2016)

- Design: open-label, randomised trial conducted at 13 sexual health clinics in England.
- Population: HIV-negative men or transgender women (male sex at birth) 18 years or older who have sex with men. Participants had reported anal intercourse without a condom in the previous 90 days and were likely to have anal intercourse without a condom in the next 90 days. Those with acute viral illness possibly due to HIV seroconversion and those being treated for hepatitis B were excluded. The pilot phase of the study randomised 546 people (the method of allocation suggests allocation was concealed). Regular sexual partners were encouraged to enrol together and both partners allocated to the same group to minimise the possibility of drug sharing. The median age was 35 years (29 to 43 years), 327 people (61%) were university graduates, 217 (40%) were born outside the UK and 160 (30%) were living with a partner. In the previous 12 months, 331 (64%) had been diagnosed with a sexually transmitted infection, 184 (36%) had received at least 1 course of post-exposure prophylaxis and 231 (44%) had used drugs associated with sexual disinhibition.
- Intervention and comparator: between November 2012 and April 2014, 275 people were randomised to the immediate group and 269 to the deferred group (2 people were randomised twice). In the immediate group, participants received once daily Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) starting at the enrolment visit. In the deferred group, once daily Truvada was planned to be started after a deferral period of 1 year. There was no screening visit. At enrolment, or 1 year later for people in the deferred group, participants were prescribed 30 tablets. An appointment was made within 1 month to check safety and tolerability and to prescribe 90 tablets. Participants were then asked to attend every 3 months, where they were given an HIV test, screened for sexually transmitted infections and hepatitis

C if susceptible. Interventions to reduce risk were offered according to routine practice at the clinic. Participants were asked to complete monthly questionnaires and daily diaries about adherence and sexual behaviour. There were 243-person years of follow-up for the immediate group and 222-person years for the deferred group. The study was originally designed with a sample size of 5000 participants (with an arbitrary 10% in the pilot phase) but after an interim review by an independent data monitoring committee found a significantly increased risk of HIV infection in the deferred group, once daily Truvada was offered to all participants in the deferred group who had not yet had this opportunity (n=163), and the larger trial was not required (Dolling et al. 2016).

- Outcomes: the primary outcome was the time to accrual of 500 participants and retention. The secondary outcomes were HIV infection between randomisation and month 12, safety, adherence, and risk compensation. Safety was assessed by serious adverse events attributable to the study drug, adverse events that lead to interruption or cessation of the study drug, renal function estimated using serum creatinine at 12 months, frequency of viral resistance in men who acquire HIV. Adherence was assessed by the proportion of doses taken according to self-report, proportion of days covered according to dispensing records, and presence of active drug in blood in a subset of participants. Risk compensation was assessed by number of sexual partners with whom unprotected anal intercourse took place, number of acts of anal intercourse (protected and unprotected), proportion of acts of anal intercourse protected by either condom, PrEP or both, and new sexually transmitted infections.

Table 3 Summary of PROUD study (McCormack et al. 2016)

	PrEP with emtricitabine/ tenofovir disoproxil 200 mg/ 245 mg (Truvada) commenced immediately on study entry	PrEP deferred (no study drug)	Analysis
Randomised	n=275	n=269	
Efficacy (modified ITT population; emergent HIV infection)	n=268 (5 people randomised had no HIV test after enrolment, 2 were infected at enrolment)	n=255 (13 people randomised had no HIV test after enrolment, 1 was infected at enrolment)	

Secondary outcome: incidence of documented HIV seroconversion	3 people had emergent HIV infection 1.2 cases per 100 person-years	20 people had emergent HIV infection 9.0 cases per 100 person-years	Rate difference 7.8 per 100 person-years (90% CI 4.3 to 11.3); p=0.0001 RRR 86% (90% CI 64% to 96%) NNT 13 (90% CI 9 to 23) over 1 year
Safety	n=275	n=269	
People interrupting or missing doses because of adverse events	8% (21/275)	Participants in this group did not receive study drug. Adverse events not reported	
People reporting any serious adverse event	10% (27/275)	Participants in this group did not receive study drug. Adverse events not reported	
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; p, p value; RRR, relative risk reduction			

IPERGAY study (Molina et al. 2015)

- Design: randomised, double-blind, placebo-controlled trial conducted in France and Canada.
- Population: HIV-negative men or transgender women (male sex at birth) aged 18 years or older who have sex with men and are at high risk for HIV infection. This was defined as a history of unprotected anal sex with at least 2 partners during the past 6 months. Exclusion criteria included testing positive for hepatitis B, chronic infection with hepatitis C and a creatine clearance of less than 60 ml per minute. In total, 445 people were screened for inclusion in the trial and 414 were randomised (the method of allocation concealment is unclear). The median age was 35 years, 73% of people were not in a couple and the median number of partners in the past 2 months was 8 (interquartile range 5–17).

- Intervention and comparator: 206 people were randomised to receive a fixed-dose combination of emtricitabine/tenofovir disoproxil 200 mg/245 mg (Truvada) 'on demand' and 208 people to placebo. People were instructed to take a loading dose of 2 tablets with food 2 to 24 hours before sex, followed by a third tablet 24 hours after the first drug intake and a fourth tablet 24 hours later. In case of multiple consecutive episodes of sexual intercourse, people were instructed to take 1 tablet daily until the last sexual intercourse and then to take the 2 post-exposure tablets. When resuming pre-exposure prophylaxis, people were instructed to take a loading dose of 2 tablets unless the last drug intake was less than 1 week earlier, when they were instructed to take 1 tablet. This was in addition to a comprehensive package of prevention services including risk-reduction counselling, condoms, and sexually transmitted infection management. Vaccination against hepatitis A and B was also offered to all susceptible people. Study visits were 4 and 8 weeks after enrolment, and every 8 weeks after that. These included drug dispensing (with enough tablets to cover daily use), pill count, adherence counselling, HIV testing and biochemical analyses. Before each visit, participants were asked to complete a computer-assisted structured interview at home about their lifestyle, sexual behaviour and adherence. At enrolment and every 6 months, participants were screened for sexually transmitted infections. After an interim review by an independent data monitoring committee, the placebo group was discontinued and all study participants were offered 'on-demand' emtricitabine/tenofovir disoproxil 200 mg/245 mg (Truvada). There was a total follow-up time of 431-person years, with a median follow-up of 9.3 months (interquartle range 4.9 to 20.6 months). The study is ongoing with an open-label design.
- Outcomes: the primary end point was the diagnosis of HIV infection. Other endpoints included adherence (from pill counts, computer-assisted structured interviews and detectable drug levels) and safety assessed by adverse events.

Table 4 Summary of IPERGAY study (Molina et al. 2016)

	Emtricitabine/tenofovir disoproxil 200 mg/245 mg (Truvada) 'on demand'	**Placebo**	**Analysis**
Randomised	n=206	n=208	
Efficacy (modified ITT population; emergent HIV infection)	n=199 (7 people randomised did not receive intervention, including 1 infected at enrolment)	n=201 (7 people randomised did not receive intervention, including 2 infected at enrolment)	

Primary outcome: incidence of documented HIV seroconversion	2 people had emergent HIV infection 0.9 cases per 100 person-years	14 people had emergent HIV infection 6.6 cases per 100 person-years	RRR 86% (95% CI 40% to 98%, p=0.002)
Safety	n=199	n=201	
People reporting any adverse event	93% (186/199)	90% (181/90)	p=0.21
People reporting any serious adverse event	10% (20/199)	8% (17/201)	p=0.58
People with gastrointestinal adverse events	14% (28/199)	5% (10/201)	p=0.002
People with elevated creatinine (any grade)	18% (35/199)	10% (20/201)	p=0.03
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention to treat; p, p value; RRR, relative risk reduction			

Clinical effectiveness

Effect of emtricitabine and tenofovir disoproxil (Truvada) on HIV acquisition

In this evidence summary, 3 of the 4 randomised trials reviewed evaluated the efficacy and safety of Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for pre-exposure prophylaxis (PrEP) in HIV-negative men or transgender women who have sex with men (iPrEx, PROUD and IPERGAY). People with high-risk sexual behaviour for HIV infection were recruited, for example those who had reported recent anal intercourse without condoms, recent anal intercourse with multiple partners, and recent diagnosis of a sexually transmitted infection. In all these trials, Truvada was given in addition to a comprehensive package of prevention services including HIV testing, risk-reduction counselling, condoms, and sexually transmitted infection management.

In the first study, iPrEx (Grant et al. 2010; which had a median follow-up of 1.2 years), Truvada once daily reduced the relative risk of acquiring HIV infection by 44% compared with placebo. In the Truvada group 36/1224 had emergent HIV infection and in the placebo group this was 64/1217

(hazard ratio [HR] 0.56; 95% confidence interval [CI] 0.37 to 0.85, p=0.005; relative reduction 44% (95% CI 15% to 63%). However, efficacy was strongly correlated with adherence (see section below). In a secondary analysis of the iPrEx study (Buchbinder et al. 2014), the HIV incidence in the placebo group was calculated at 3.9 cases per 100 person-years, and the overall number needed to treat (NNT) per year was 62 (95% CI 44 to 147).

In the open-label PROUD study (McCormack et al. 2016; which was conducted in England and had 243-person years of follow up in the immediate PrEP group and 222-person years of follow-up in the deferred PrEP group), immediate PrEP with Truvada once daily reduced the relative risk of acquiring HIV infection by 86% compared with no prophylaxis in the deferred group. There were 3/268 people with emergent HIV infection in the group randomised to Truvada immediately on study entry compared with 20/255 in the group where Truvada was deferred. This equated to a rate difference of 7.8 per 100 person-years (90% CI 4.3 to 11.3; 1.2 cases per 100 person-years in the immediate group compared with 9.0 cases per 100 person-years in the deferred group; relative risk reduction [RRR] 86%, 90% CI 64% to 96%; NNT 13 per year, 90% CI 9 to 23).

In IPERGAY (Molina et al. 2015; which was conducted in France and Canada and had a median follow-up of 9.3 months), Truvada was given 'on demand' before and after sexual activity rather than regularly once daily. Participants took a median of 15 tablets per month (interquartile range 11 to 21 in the Truvada group). 'On-demand' Truvada reduced the relative risk of acquiring HIV infection by 86% compared with placebo. In the Truvada group 2/199 had emergent HIV infection, a rate of 0.9 cases per 100 person-years, and in the placebo group this was 14/201, a rate of 6.6 cases per 100 person-years (RRR 86%; 95% CI 40% to 98%, p=0.002). This equates to a rate difference of 5.7 cases per 100 person-years or an NNT of 18 per year (95% CI 15 to 38).

The fourth randomised trial reviewed in this evidence summary (Partners PrEP; Baeten et al. 2012 and Baeten et al. 2014) evaluated the efficacy and safety of Truvada for PrEP in HIV-negative individuals from serodiscordant heterosexual couples in Kenya and Uganda. This study (with an initial median follow-up of 23 months, published in 2012) found Truvada once daily reduced the relative risk of acquiring HIV infection by 75% compared with placebo. There were 13/1568 people with emergent HIV infection in the Truvada group, a rate of 0.50 cases per 100 person-years, compared with 52/1568 in the placebo group, a rate of 1.99 cases per 100 person-years (HR 0.25; 95% CI 0.13 to 0.45, p<0.001). This equates to a rate difference of 1.49 cases per 100 person-years or an NNT of 68 per year (95% CI 58 to 92).

Partners PrEP also had a tenofovir disoproxil only arm, and after re-randomisation of people in the placebo group to either once daily tenofovir disoproxil only or once daily Truvada, no statistically significant difference was found between these groups. In the Truvada group 21/2208 had

emergent HIV infection, a rate of 0.48 cases per 100 person-years, and in the tenofovir disoproxil only group 31/2207 had emergent HIV infection, a rate of 0.71 cases per 100 person-years (HR 0.67; 95% CI 0.39 to 1.17, p=0.16). However, the European Public Assessment Report (EPAR) states that because there was a trend favouring Truvada over tenofovir alone, and tenofovir is the main driver of the safety profile of Truvada, there is no strong reason to select tenofovir alone when it could be associated with lesser protection.

Uptake and adherence

In the iPrEx study, once-daily Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) reduced the risk of acquiring HIV infection by 44%, which was not as high as had been hypothesised and was less than that seen in other studies. Although the reported use of Truvada was high (pill count suggested a median range of 89% to 95% use), drug exposure was substantially lower in a pre-specified subgroup analysis. Among people in the active treatment group, emtricitabine or tenofovir was detected in only 3 of 34 people (9%) with HIV infection and 22 of 43 people (51%) who were HIV-negative. In the people with detectable study drug levels, the relative reduction in the risk of HIV was 92% (95% confidence interval, 40% to 99%, p<0.001) compared with those with no detectable drug levels.

In an open-label extension of the iPrEx study (Grant et al. 2014), which also included HIV-negative men and transgender women who have sex with men previously enrolled in 2 other studies (ATN 082 and the US Safety Study [with tenofovir disoproxil only]), 1230 (77%) of 1603 people wanted to receive PrEP according to a computer-based self-interview. Reasons for not requesting PrEP were concerns about side effects, not wanting to take a tablet every day, not liking taking tablets, a preference for other prevention methods, fear that people may think they have HIV and fear that people will know they have sex with men. Receiving PrEP was statistically significantly higher in people who reported non-condom receptive anal intercourse and had herpes infection. Of all people who received PrEP and had drug exposure tested, drug was detected in 847 (71%) of people. Drug concentrations were higher among older people, those with more years of schooling, non-condom receptive anal intercourse, more sexual partners, a history of syphilis or herpes, or any HIV-positive sexual partner. There were no HIV infections noted at visits where blood tenofovir diphosphate concentrations were consistent with the use of 4–7 tablets per week (seen in 33% of visits among the 'on-PrEP' group): HR for infection 0.00 (95% CI 0.00 to 0.14) compared with the concurrent 'off-PrEP' group after adjustment for baseline HIV risk factors). The drug concentration associated with a 90% reduction in risk relative to the off-PrEP group was consistent with the use of 2–3 tablets per week The most common pattern of PrEP use was clinically significant use followed by discontinuation; intermittent use was not common.

In the immediate Truvada group in the PROUD study, sufficient study drug was prescribed for 88% of the total follow up time. Fourteen (5%) of 275 participants were prescribed no further study drug after the initial prescription. However, tenofovir was detected in all 52 sampled participants who reported they were taking PrEP.

In the IPERGAY study of 'on demand' PrEP, participants took a median of 15 tablets per month in both the Truvada and placebo groups (interquartile range 11 to 21 in the Truvada group and 9 to 21 in the placebo group). However, individual patterns of tablet use showed large interpatient and intrapatient variability over time. Study drug levels were measured in the first 113 participants enrolled and, in the active treatment group, rates of detection for tenofovir diphosphate and emtricitabine were 86% and 82% respectively. However, based on computer-assisted structured interviews, although 43% of people took the assigned drug correctly during the most recent sexual intercourse, 29% took a suboptimal dose and 28% did not take the assigned drug at all.

The summary of product characteristics (SPC) for Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) emphasises the importance of adherence, stating that people should be counselled to strictly adhere to the recommended dosing schedule because the effectiveness of Truvada in reducing the risk of acquiring HIV is strongly correlated with adherence.

Sexual practices

In the iPrEx study, self-reported sexual practices were similar in the Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) and placebo groups at all time points. However, one purpose of using placebo in the placebo-controlled RCTs of Truvada was to avoid confounding bias due to risk compensation (participants knew they might be taking an inactive treatment), and in both groups a comprehensive package of prevention services was given. The self-reported total number of sexual partners decreased and the percentage who used a condom increased in both groups after enrolment in the study. There were also no differences between groups in the numbers of participants with sexually transmitted infections. In the open-label follow-up of this study and others (Grant et al. 2014), the self-reported total number of sexual partners and non-condom anal intercourse decreased during follow-up in the group receiving PrEP and in the group not receiving PrEP. Syphilis incidence was also similar in both groups (7.2 infections per 100 patient-years in the group receiving PrEP and 5.4 infections per 100 patient-years in the group not receiving PrEP; hazard ratio 1.35, 95% CI 0.83 to 2.19).

In the PROUD study, where no placebo was given and people knew whether they were taking PrEP or not, questionnaires about sexual behaviour in the previous 90 days were completed and returned by 271/275 people in the immediate Truvada group at baseline (212 of them at 1 year). In

the deferred group questionnaires were completed and returned by 263/269 people at baseline (194 of them at 1 year). At 1 year, there was no difference between groups in the total number of sexual partners (p=0.57) but more people in the immediate Truvada group reported receptive anal sex with 10 or more partners without a condom (21% compared with 12%, p=0.03). Bacterial sexually transmitted infections (gonorrhoea, chlamydia and syphilis) were more common in the immediate group than in the deferred group who were taking no prophylaxis (57% compared with 50%), but when adjusted for the number of screens for infections (which was higher in the immediate group) there was no statistically significant difference between the groups (odds ratio 1.07; 90% CI 0.78 to 1.46, p=0.74). There were 6 cases of hepatitis C infection, 3 in each group. Antiretroviral post-exposure prophylaxis was prescribed to 12 people (14 courses) in the immediate Truvada group and 85 people (174 courses) in the group receiving no prophylaxis.

In the IPERGAY study, self-reported sexual practices did not change overall during the study period compared with baseline in either the active or placebo group. There were no statistically significant between-group differences in the total number of episodes of intercourse or of episodes of receptive anal intercourse without a condom. There was a slight difference in average number of sexual partners in the previous 2 months (8 in the Truvada group and 7.5 in the placebo group, p=0.001). New sexually transmitted infections occurred during follow-up in 41% of the Truvada group and 33% of the placebo group (p=0.10). During follow-up, overall, 20% of participants acquired chlamydia infections, 22% gonorrhoea, 10% syphilis and 1% hepatitis C.

HIV-drug-resistance to tenofovir or emtricitabine

In the iPrEx study, among 10 people who had HIV infection at enrolment, 3 people had an emtricitabine-resistant infection and none had a tenofovir-resistant infection. The SPC for Truvada states that M184I and M184V mutations were detected in the HIV of 2 of 2 people in the Truvada group and 1 of 8 people in the placebo group. Among 100 people who became infected with HIV during the study (36 of whom were randomised to active treatment), no emtricitabine or tenofovir resistance was detected. However, in the open-label follow-up of the iPrEx study and others (Grant et al. 2014), 1 person who became infected with HIV whilst on PrEP had an emtricitabine-resistant infection.

In the Partners PrEP study, among 8 people in the tenofovir disoproxil alone or Truvada groups who were infected with HIV at baseline, 1 person had an emtricitabine-resistant infection in the Truvada group and 1 person had a tenofovir-resistant infection in the tenofovir disoproxil only group. The SPC for Truvada states that the M184V mutation was detected in the HIV of 1 of 3 people in the Truvada group and the K65R mutation was detected in the HIV of 1 of 5 people in

the tenofovir disoproxil only group. No participants who acquired HIV after randomisation were infected with a resistant HIV strain.

In the PROUD study, in the group randomised to start Truvada immediately on study entry, 2 people had HIV infection at baseline and 1 tested positive for HIV at the 4-week visit. Of these 3 people, 2 developed an emtricitabine-resistant mutation. No resistance was detected in the 2 people who developed HIV at later time points and no participants developed a tenofovir-resistant mutation.

In the IPERGAY study, none of the 16 people who developed HIV infection after enrolment had resistant mutations to tenofovir or emtricitabine.

The WHO systematic review and meta-analysis of oral PrEP for all populations (Fonner et al. 2015), which included 14 RCTs and 3 observational open-label extension projects of Truvada or tenofovir disoproxil alone for PrEP, concluded that the risk of drug resistance was low overall, and occurred mainly among people who were acutely infected with HIV when PrEP was started. However, although mathematical models inform the risk of resistance, their results rely on data from clinical trials and make assumptions about the risk of selection of drug-resistant virus during PrEP. How the implementation of PrEP on a larger, population-based scale affects resistance overall is unknown, and WHO guidelines from 2016 concluded that active surveillance may be required. This is already in place in the UK through the HIV resistance database.

The SPC states that Truvada alone does not constitute a complete regimen for treating HIV, and resistant mutations have emerged in people with undetected HIV infection who are only taking Truvada. Truvada for PrEP is contraindicated in people with unknown or positive HIV-1 status; and if clinical symptoms consistent with acute viral infection are present, and recent (< 1 month) exposures to HIV are suspected, use of Truvada for PrEP should be delayed for at least 1 month and HIV status reconfirmed before starting Truvada.

Safety and tolerability

The safety data such as that listed in the summary of product characteristics (SPC) for Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) are largely derived from its use as treatment in people who are HIV positive. The risk of adverse effects when Truvada is used for pre-exposure prophylaxis (PrEP) is less well described, although some information is available in the SPC. The following sections give information on safety data that is relevant to renal safety, bone safety, hepatitis and general tolerability.

Renal safety

The SPC for Truvada states that emtricitabine and tenofovir are primarily excreted by the kidneys, and renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil for treating HIV infection. The SPC recommends that creatinine clearance is calculated in all people before initiating therapy with Truvada for either treatment or prevention and that renal function (creatinine clearance and serum phosphate) is monitored, after 2 to 4 weeks of use, after 3 months of use and every 3 to 6 months thereafter in people without renal risk factors. In people at risk of renal impairment, more frequent monitoring of renal function is required. Truvada for PrEP has not been studied in people with creatinine clearance <60 ml/min, and is therefore not recommended for use in this population. If serum phosphate is <0.48 mmol/litre or creatinine clearance is decreased to <60 ml/min in anyone receiving Truvada for PrEP, renal function should be re-evaluated within 1 week, and interrupting use considered. Use of Truvada should be avoided with concurrent or recent use of a nephrotoxic medicine or, if this is unavoidable, renal function should be monitored weekly. Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in people infected with HIV treated with tenofovir disoproxil in combination therapy and with risk factors for renal dysfunction. If Truvada is co-administered with an NSAID, renal function should be monitored adequately.

In the iPrEx study, elevated creatinine levels were seen in 2% of the Truvada group and 1% of the placebo group (p=0.08). A total of 10 elevations led to discontinuation of the study drug (7 in the Truvada group and 3 in the placebo group). All elevations resolved after the study drug was stopped and in 9 people the study drug was restarted. In a further analysis of the renal data from iPrEx, Solomon et al. 2014 concluded that Truvada was associated with a mild, reversible non-progressive decrease in creatinine clearance. There was a statistically significant decrease in creatinine clearance from baseline in the Truvada group compared with the placebo group, which was first seen at week 4 (mean change −2.4 ml/min with Truvada compared with −1.1 ml/min with placebo; p=0.02). This persisted through treatment and resolved after drug treatment was stopped.

Elevated creatinine levels were also seen in 18% of the Truvada group and 10% of the placebo group (p=0.03) in the IPERGAY study, but none led to discontinuation of the study drug. In the open-label follow-up of the iPrEx study and others (Grant et al. 2014), which included 1230 people who received PrEP, there were 3 confirmed cases of increased serum creatinine.

In PROUD, 3/275 people in the immediate Truvada group interrupted treatment because of high creatinine levels, but the study drug was restarted in all these people. In Partners PrEP, elevated

creatinine was reported as an adverse event in 1% of people in all groups (tenofovir disoproxil alone, Truvada and placebo).

Bone safety

The SPC for Truvada states that small decreases in bone mineral density of the hip and spine were seen in a study of treatment with tenofovir disoproxil in people who were antiretroviral-naive, but there was no increased risk of fractures or evidence for clinically relevant bone abnormalities. In prospective and cross-sectional studies, the most pronounced decreases in bone mineral density were seen in people treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy.

The SPC also states that in clinical studies of people uninfected with HIV, small decreases in bone mineral density were seen. In a sub-study of iPrEx (Mulligan et al. 2015), DXA scans of the lumbar spine and hip were performed on 247 people in the Truvada group and 251 people in the placebo group at baseline and at 24-week intervals. By 24 weeks there was a statistically significant decrease in bone mineral density of −0.91% in the spine (p=0.001) and −0.61% in the hip (p=0.001) with Truvada compared with placebo. In people with drug levels indicating consistent dosing, bone mineral density loss was −1.42% in the spine and −0.85% in the hip. Among all people in the main iPrEx study there were fractures in 1.7% of the Truvada group and 1.4% of the placebo group (p=0.62).

Hepatitis

The SPC for Truvada states that people infected with HIV with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. The safety and efficacy of Truvada for PrEP in people with hepatitis B or C has not been established. Emtricitabine and tenofovir individually and in combination have shown activity against hepatitis B virus in pharmacodynamic studies, and discontinuation of Truvada in people infected with hepatitis B virus may be associated with severe acute exacerbations of hepatitis. The SPC states that people with hepatitis B virus who stop treatment with Truvada should be closely monitored for several months. In people with advanced liver disease or cirrhosis, stopping treatment is not recommended because an exacerbation of hepatitis may lead to hepatic decompensation.

The SPC also states that the safety and efficacy of Truvada has not been established in people with significant underlying liver disorders. People with pre-existing liver dysfunction have an increased

risk of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice.

Tolerability

The most frequently reported adverse reactions considered possibly or probably related to treatment with emtricitabine or tenofovir disoproxil fumarate listed in the SPC for Truvada are nausea (12%) and diarrhoea (7%). The SPC states that no new adverse reactions to Truvada were identified from the iPreX and Partners PrEP studies, and that the most frequent adverse reaction reported in the Truvada group in the iPrEx study was headache (1%).

In iPrEx, nausea was reported in 2% of the Truvada group and 0.7% of the placebo group (p=0.04); and unintentional weight loss in 2% and 1% of groups, respectively (p=0.04). Gastrointestinal adverse events were reported in 14% of the Truvada group and 5% of the placebo group (p=002) in IPERGAY. In the Partners Prep study, there were increased reports of gastrointestinal side effects and fatigue with Truvada, mainly during the first month. In this study, neutropenia was also seen more commonly in the Truvada group than in the placebo group (18% compared with 13%; p<0.001).

In PROUD, 8% of people (21/275) in the immediate Truvada group interrupted or missed doses because of adverse events (the deferred group received no study drug and adverse events were not reported). These were most commonly nausea, headache and arthralgia. Study drug was restarted in 20 of these people. Serious adverse events were reported in 27 people, but none of these were attributed to study medication. In the open-label follow-up of the iPrEx study and others (Grant et al. 2014), which included 1230 people who received PrEP, drug treatment was interrupted 3.7% of the time because of side effects, most commonly nausea or abdominal pain.

The WHO systematic review and meta-analysis of oral PrEP for all populations (Fonner et al. 2015), which included 14 RCTs and 3 observational open-label extension projects of Truvada or tenofovir alone for PrEP, concluded that across 10 RCTs comparing PrEP with placebo there was no difference in the rate of adverse events overall (RR 1.01; 95% CI 0.99 to 1.03, p=0.27). Several studies reported small but significant decreases in renal function, and small decreases in liver functioning and bone mineral density were also seen in some studies.

The SPC states that use of Truvada is not recommended in children and young people below 18 years of age because insufficient safety data are available. Truvada has also not been studied in people over the age of 65 years, and the SPC advises caution because elderly people are more likely to have decreased renal function.

Evidence strengths and limitations

Of the 4 randomised trials reviewed in this evidence summary, 3 evaluated Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for pre-exposure prophylaxis (PrEP) in HIV-negative men or transgender women who have sex with men. These were the iPrEx study conducted in Peru, Ecuador, Brazil, US, Thailand and South Africa; the PROUD study conducted in England; and the IPERGAY study conducted in France and Canada.

The iPrEx study was a well-conducted RCT; however no information on allocation concealment was given. There were also concerns about adherence, in that the reported use of Truvada was high but drug exposure measured objectively in a pre-specified subgroup analysis was much lower. Follow-up was for a median of 1.2 years, and the HIV incidence in the placebo group was 3.9 per 100 person-years, with an NNT of 62 per year (Buchbinder et al. 2014).

The PROUD study is directly relevant to the use of Truvada for PrEP in the UK; having been conducted in 13 sexual health clinics in England. The design has strengths and limitations. Its open-label, real-world design represents how PrEP is likely to be used in routine clinical practice, taking account of adherence to a drug known to have efficacy and any consequent change in sexual practice. However, there is an increased risk of bias because participants and clinicians knew the allocation of study treatment. The lack of data on adherence, in particular, is also a limitation. Sexual behaviour was assessed through questionnaires, but these were at specific time points (baseline and 1 year) because there was a low completion rate of monthly questionnaires, and it is not possible to assess precisely how participants matched adherence to risk.

The incidence of HIV infection was 9.0 cases per 100 person-years in the control group in the PROUD study. The authors suggest that the national rate of HIV incidence among men who have sex with men attending sexual health clinics in the UK is closer to 1.3 cases per 100 person-years, so the population in PROUD was highly selective despite broad eligibility criteria. In a population with a lower incidence of HIV infection, assuming the same relative risk reduction would apply, then the number needed to treat (NNT) would be higher than the figure of 13 seen in the PROUD study. Additionally, this study was stopped early because of a significantly increased risk of HIV infection in the deferred group, therefore follow-up in the randomised phase was limited (the open-label extension phase of PROUD is ongoing). If adherence diminishes over time, as was seen in the open-label follow-up of the iPrEx study and others (Grant et al. 2014), shorter follow-up could exaggerate the efficacy of PrEP. In the PROUD study, Truvada reduced the relative risk of acquiring HIV infection by 86% compared with a relative risk reduction of 44% in the iPrEx study where adherence levels were questioned.

The IPERGAY study also found that Truvada reduced the relative risk of acquiring HIV infection by 86%, but the authors suggest that the short follow-up (median of 9.3 months) could have exaggerated this estimate because of high initial adherence. The incidence of HIV infection was also high at 6.6 cases per 100 person-years in the placebo group. IPERGAY was a double-blind, placebo-controlled trial RCT but no information on allocation concealment was given and the study was also stopped early because of a significantly increased risk of HIV infection in the placebo group. IPERGAY assessed 'on demand' use of Truvada rather than once daily use as in the licence extension for Truvada for PrEP. Participants in IPERGAY took a median of 15 tablets per month, but individual patterns of tablet use showed large interpatient and intrapatient variability over time. Despite the persistence of the effectiveness of Truvada with on demand use in IPERGAY, it is unclear how this would translate to a population that may be taking Truvada more intermittently than seen in this study.

The fourth randomised trial (Partners PrEP) evaluated Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for PrEP in HIV-negative heterosexual men and women. The incidence of HIV infection was lower in this study at 1.99 cases per 100 person-years in the placebo group, and follow-up was a median of 23 months. Partners PrEP was a double-blind, placebo-controlled RCT that was also stopped early because of a significantly increased risk of HIV infection in the placebo group. However, it was conducted in Africa and although there is no obvious reason why biological efficacy would not have been the same, the findings may be less relevant to a UK population. Other trials of Truvada in heterosexual men and women have been published, but these were also conducted in Africa (VOICE, TDF2 and FEM-PrEP).

The WHO systematic review included 1 study of PrEP in people who inject drugs (the Bangkok tenofovir study). However, this was with tenofovir disoproxil only and was conducted in substance-misuse clinics in Thailand, which may not be representative of the population of people who inject drugs in the UK.

Context

Alternative treatments

Prevention strategies for HIV include early diagnosis of HIV infection through HIV testing, antiretroviral therapy for those diagnosed positive to reduce onward transmission (treatment as prevention [TasP]), correct and consistent condom use, and addressing the wider determinants of high-risk sexual behaviour. Using antiretroviral agents to prevent HIV acquisition in those who are HIV negative (pre-exposure prophylaxis [PrEP]) is also an option (Public Health England, situation report 2015).

In the European AIDS Clinical Society (EACS) guidelines from 2015 the recommended PrEP regimen is 1 tablet of emtricitabine/tenofovir disoproxil 200 mg/245 mg once daily. For men who have sex with men with high-risk sexual behaviour, these guidelines recommend 'on demand' emtricitabine/tenofovir disoproxil 200 mg/245 mg may be given. WHO guidelines from 2016 recommend oral PrEP containing tenofovir disoproxil (no particular regimen is recommended).

Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) is the only antiretroviral product that is licensed for use as PrEP in the UK; and the licence extension is for once-daily use. Neither 'on demand' use of Truvada, nor tenofovir disoproxil (Viread) or emtricitabine (Emtriva) as separate tablets, is licensed for PrEP. In relation to Truvada, the relevant compound patents relate to tenofovir disoproxil and salts, which expires in July 2017 and tenofovir disoproxil fumarate, which expires in July 2018. A supplementary protection certificate has also been granted in relation to Truvada which expires in February 2020 (a challenge of this is pending before the UK Court; personal communication, Gilead, September 2016).

The BHIVA-BASHH 2016 position statement on PrEP includes information on other HIV prevention strategies including condoms, male circumcision, post-exposure prophylaxis following sexual exposure (PEPSE), antiretroviral therapy for HIV-positive partners, and PrEP regimens other than oral emtricitabine and tenofovir disoproxil (for example oral tenofovir only, tenofovir vaginal or rectal gel and dapivirine intravaginal ring). More detail on these alternative prevention strategies is not covered in this evidence summary.

Costs of alternative treatments

Drug	Dose	30-day cost, excluding VAT
emtricitabine/tenofovir disoproxil 200 mg/245 mg (Truvada)	1 tablet once daily[a]	£355.73[b]
emtricitabine/tenofovir disoproxil 200 mg/245 mg (Truvada)	'on demand' (2 tablets 2-24 hours before each sexual intercourse, followed by 1 tablet 24 and 48 hours after the first drug intake)[c]	£177.87[d]

tenofovir disoproxil 245 mg (Viread) and emtricitabine 200 mg (Emtriva) as separate tablets	1 tablet of each once daily[e]	£343.37[b]
tenofovir disoproxil 245 mg (Viread) only	1 tablet once daily[f]	£204.39[b]

[a] Based on the dosage regimen in the licence extension for the use of Truvada in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk (Truvada summary of product characteristics). Also dosing regimen recommended in the European AIDS Clinical Society (EACS) guidelines from 2015.

[b] Costs taken from MIMS, August 2016 (excluding VAT). However, Truvada, Viread and Emtriva are currently purchased at discounted net price for treating HIV through the Commercial Medicines Unit (CMU) regional framework (personal communication, Gilead, June 2016).

[c] Alternative dosing regimen recommended for men who have sex with men with high-risk sexual behaviour in the European AIDS Clinical Society (EACS) guidelines from 2015 based on the dosing regimen used in the IPERGAY study. This dosing regimen for Truvada is not licensed.

[d] Based on costs for 15 tablets per month which was the median number of tablets per month in the IPERGAY study (although large interpatient and intrapatient variability in tablet use). Costs taken from MIMS, August 2016 (excluding VAT). However, Truvada is currently purchased at discounted net price for treating HIV through the Commercial Medicines Unit (CMU) regional framework (personal communication, Gilead, June 2016).

[e] Neither tenofovir disoproxil (Viread) nor emtricitabine (Emtriva) are licensed for PrEP.

[f] Based on the dosing regimen in the Partners PrEP study which had a tenofovir only arm. Tenofovir disoproxil (Viread) is not licensed for PrEP.

Cost-effectiveness studies

Fully published data on UK cost-effectiveness analyses of Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) for PrEP are limited.

Several meeting abstracts have been published including Ong et al. 2015 (Public Health England; abstract only) which estimated the cost and cost-effectiveness of a daily oral PrEP programme in 10,000 high-risk men who have sex with men attending genitourinary medicine clinics in England; and a further study which explored the clinic costs of introducing PrEP (Ong et al. 2016; Public Health England; abstract only). A UK cost-effectiveness analysis of PrEP in men who have sex with men who engage in condomless sex has also been conducted by Cambiano et al. 2015 (abstract

only), which is expected to be published in full in 2016 (personal communication with the authors; August 2016). A mathematical modelling study, Punyacharoensin et al. 2016 which estimated the effect of 7 different HIV interventions (including increasing rates of HIV testing, test-and-treat programmes, PrEP and sexual behavioural changes) individually and simultaneously on the prevention of HIV infection in men who have sex with men in the UK has also been published.

All these analyses suggest that the cost-effectiveness of PrEP is very sensitive to key variables such as HIV incidence, uptake, adherence, trends in condomless sex, and drug costs. The WHO guidelines from 2016 suggest that giving priority for the use of PrEP to the people most at risk of acquiring HIV infection could increase its impact.

Estimated impact for the NHS

Likely place in therapy

European AIDS Clinical Society (EACS) guidelines from 2015 and WHO guidelines from 2016 both recommend pre-exposure prophylaxis (PrEP) for people at high-risk of acquiring HIV infection in combination with other preventive interventions, including the use of condoms. The European guidelines recommend PrEP for HIV-negative men who have sex with men and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not on treatment. These guidelines also state that PrEP may be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and are likely to have HIV-positive partners who are not on treatment. The WHO guidelines recommend PrEP as an additional prevention choice for people at 'substantial risk' of HIV infection (populations with a HIV incidence of around 3 cases per 100 person-years or higher), such as men who have sex with men, transgender women, and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection.

In May 2016, BHIVA and BASHH published a position statement on PrEP in the UK, which recommends that PrEP be made available within a comprehensive HIV prevention package to:

- men who have sex with men, trans men and trans women who are engaging in condomless anal sex
- HIV-negative partners who are in serodiscordant heterosexual and same-sex relationships with a HIV-positive partner whose viral replication is not supressed
- other heterosexuals considered to be at high risk.

At present there is no publicly funded PrEP programme in the UK. See the NHS England website for current information around the commissioning of PrEP. Although some studies have looked at tenofovir disoproxil only for PrEP, the majority (particularly those in men who have sex with men) have used Truvada (emtricitabine/tenofovir disoproxil 200 mg/245 mg) as a single tablet. Truvada is the only antiretroviral product that is licensed for use as PrEP in the UK. The licence extension is for once-daily use: 'on demand' use of Truvada, tenofovir disoproxil (Viread) alone, or with emtricitabine (Emtriva) as separate tablets, is not licensed for PrEP.

Evidence for the use of Truvada for PrEP that is most relevant to the UK population relates to its use by men or transgender women who have sex with men. This group in particular has ongoing high rates of HIV transmission and acquisition, and the Public Health England situation report on HIV emphasises the need for high impact, appropriately tailored combination prevention strategies and programmes for this group. Both the Public Health England report and the BHIVA-BASHH position statement stress that PrEP is only one of several prevention tools for HIV, and early diagnosis through testing, antiretroviral therapy for people who are HIV-positive to reduce the risk of onward transmission, correct and consistent condom use, and addressing the wider determinants of poor sexual health among this population are also important.

There is little doubt that Truvada is effective in reducing HIV acquisition in high-risk people who are HIV-negative. However, issues relating to uptake, adherence, sexual behaviour, drug resistance, safety, prioritisation for prophylaxis and cost-effectiveness, are also important to consider, especially at a population level.

High treatment adherence during periods of risk is essential for Truvada to prevent HIV infection, and the summary of product characteristics emphasises that people should be counselled to strictly adhere to the recommended dosing schedule. In the iPrEx study, there were particular concerns that drug exposure was low. Reasons why PrEP might not be taken include concerns about side effects, not wanting to take a tablet every day, and a fear that people may think the person has HIV (Grant et al. 2014). In the open-label follow-up of the iPrEx study, the most common pattern of PrEP use was clinically significant use followed by discontinuation; intermittent use was not common. When Truvada was taken 'on demand' in the IPERGAY study, individual patterns of tablet use showed large interpatient and intrapatient variability over time. The WHO guidelines from 2016 state that support for adherence should include information that PrEP is highly effective when used, and if people are advised that side effects that may be experienced in the first few weeks, such as nausea, are typically self-limiting they could be more adherent. The WHO guidelines also refer to PrEP being needed during periods of risk rather than for life. Such periods of risk may include changes in relationship status, and leaving school or home.

There have been concerns that sexual behaviour might become more high- risk if people are taking PrEP. The trials reviewed in this evidence summary were largely reassuring in this regard, but they were short term, all but one had a placebo group (one purpose of which was to avoid confounding bias due to risk compensation), and in both the Truvada and control groups a comprehensive package of prevention services was given. It will be important to monitor sexual risk behaviour over a longer period of time in cohort studies or demonstration projects, but it could be difficult to separate the influence of PrEP use from other influencing factors on risk behaviour. Additionally, WHO guidelines from 2016 state that people who are at substantial risk of acquiring HIV are often medically underserved, and providing PrEP may give opportunities for increased access to a range of other health services. These could include regular HIV testing and screening for sexually transmitted infections and hepatitis B, and counselling and support around high-risk sexual behaviour and recreational drug and alcohol use.

A potential disadvantage of PrEP is the development and transmission of drug-resistant viruses, which could result in the loss of options for treating HIV. In the iPrEx and Partners Prep studies, people who had an undetected acute HIV infection when PrEP was initiated had the highest risk of developing drug resistance. The WHO systematic review and meta-analysis of oral PrEP for all populations (Fonner et al. 2015) concluded that the risk of drug resistance was low overall, and occurred mainly among people who were acutely infected with HIV when PrEP was started. However, it is not known how the implementation of PrEP on a larger, population-based scale affects resistance overall, and active surveillance, such as that already in place in the UK, will be important. The SPC states that Truvada for PrEP is contraindicated in people with unknown or positive HIV-1 status. It should be used only in people who have been confirmed to be HIV negative, and this should be reconfirmed at frequent intervals (for example at least every 3 months). More information on HIV testing is given in the BHIVA and BASHH position statement on PrEP.

The SPC for Truvada has cautions about renal and bone safety, and the use of Truvada in people with hepatitis B or C. There is some information on the renal effects of Truvada for PrEP from the 4 studies reviewed in this evidence summary (iPrEx, Partners PrEP, PROUD and IPERGAY), and limited information on its effects on bone mineral density from a sub-study of iPrEx, which is included in the SPC. However, more information on the renal and bone safety of Truvada in people who are not infected with HIV may only become apparent over time with use in a wider population. The SPC recommends that creatinine clearance is calculated in all people before Truvada for PrEP is started, and that it should be monitored periodically thereafter. Emtricitabine and tenofovir individually and in combination have shown activity against hepatitis B virus, and discontinuation of Truvada in people infected with hepatitis B virus may be associated with severe acute exacerbations of hepatitis. The SPC states that the safety and efficacy of Truvada for PrEP in people with hepatitis B or C has not been established.

Estimated usage

It is not possible to provide estimated usage based on the available data, since prioritisation and eligibility criteria would have a key bearing on uptake.

Relevance to NICE guidance programmes

There is no NICE guidance on pre-exposure prophylaxis for HIV. The NICE pathway on HIV testing and prevention brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. Related NICE guidance that has been published includes:

HIV testing: increasing uptake in black Africans (2011) NICE guideline PH33

HIV testing: increasing uptake in men who have sex with men (2011) NICE guideline PH34

HIV testing (2014) NICE local government briefing 21

Needle and syringe programmes (2014) NICE guideline PH52

References

ADAPT study: use of emtricitabine and tenofovir disoproxil fumarate for pre-exposure prophylaxis (PrEP). US National Institutes of Health (2016) ClinicalTrials.gov Identifier: NCT01327651 [accessed 14 July 2016]

Baeten JM, Donnell D, Ndase P et al. for the Partners PrEP study team (2012) Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. New England Journal of Medicine 367:399–410

Baeten JM, Donnell D, Mugo NR et al. for the Partners PrEP study team (2014) Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. Lancet Infectious Diseases 14: 1055–64

British Association for Sexual Health and HIV (2015) UK guideline for the use of HIV post-exposure prophylaxis following sexual exposure (PEPSE)

Buchbinder SP, Glidden DV, Liu AY et al. (2014) HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. Lancet Infectious Diseases 14: 468–75

Cambiano V, Miners A, Dunn D et al. (2015) O1: Is pre-exposure prophylaxis for HIV prevention cost-effective in men who have sex with men who engage in condomless sex in the UK? Sexually Transmitted Infections 91: A1 (oral presentation)

Choopanya K, Martin M, Suntharasamai P et al. for the Bangkok Tenofovir Study Group (2013) Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 381: 2083–90

Dolling DI, Desai M, McOwan et al. (2016) An analysis of baseline data from the PROUD study: an open-label randomised trial of pre-exposure prophylaxis. Trials 17: 163

European Aids Clinical Society. Guidelines version 8. October 2015

Fonner V, Grant R, Baggaley R. Oral pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis of effectiveness, safety, and sexual and reproductive health outcomes. Web supplement to guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Annex 2.2.3

Grant RM, Lama JR, Anderson PL et al. for the iPrEx study team (2010) Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New England Journal of Medicine 30; 363: 2587–99

Grant RM, Anderson PL, McMahan V et al. for the iPrEx study team (2014) Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infectious Diseases 14: 820–9

Grohskopf LA, Chillag KL, Gvetadze R et al. (2013) Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. Journal of Acquired Immune Deficiency Syndromes 64: 79–86

Hosek SG, Siberry G, Bell M et al. the Adolescent Trials Network for HIV/AIDS Interventions (ATN) (2013) The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. Journal of Acquired Immune Deficiency Syndromes 62: 447–56

Kibengo FM, Ruzagira E, Katende D et al. (2013) Safety, adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. PLoS One 8(9):e74314

Marrazzo JM, Ramjee G, Richardson BA et al. for the VOICE study team (2015) Tenofovir-based preexposure prophylaxis for HIV infection among African women. New England Journal of Medicine 372: 509–18

McCormack S, Dunn DT, Desai M et al. (2016) Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 387: 53–60

McCormack S, Fidler S, Waters L et al. (2016) BHIVA–BASHH Position Statement on PrEP in UK. Second Update May 2016

Molina JM, Capitant C, Spire B et al. for the ANRS IPERGAY study group (2015) On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. New England Journal of Medicine 373: 2237–46

Mulligan K, Glidden DV, Anderson PL et al. (2015) Effects of emtricitabine/tenofovir on bone mineral density in HIV-negative persons in a randomized, double-blind, placebo-controlled trial. Clinical Infectious Diseases 61: 572–80

Mutua G, Sanders E, Mugo P et al. (2012) Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. PLoS One 7(4):e33103

NHS England. Clinical Commissioning Policy: Treatment as Prevention (TasP) in HIV infected adults. July 2015

Ong KJ, Desai S, Desai M, et al. (2015) Cost and cost-effectiveness of an HIV pre-exposure prophylaxis (PrEP) programme for high-risk men who have sex with men in England: results of a static decision analytical model. Lancet 386: S16 (meeting abstract)

Ong KJ, Field N, Mitchell H et al. (2016) P073: If HIV-PrEP is made available in England, what are the resource implications for GUM clinic service providers? Sexually Transmitted Infections 92: A44 (poster presentation)

Partners Demonstration Project of PrEP and ART. US National Institutes of Health (2016) ClinicalTrials.gov Identifier: NCT02775929 [accessed 14 July 2016]

Peterson L, Taylor D, Roddy R et al. (2007) Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials 2(5): e27

Public Health England. HIV in the UK – Situation Report 2015. November 2015

Punyacharoensin N, Edmunds WJ, De Angelis D et al. (2016) Effect of pre-exposure prophylaxis and combination HIV prevention for men who have sex with men in the UK: a mathematical modelling study. Lancet HIV 3: e94–e104

Solomon MM, Lama JR, Glidden DV et al. (2014) Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. AIDS 28: 851–9

Thigpen MC, Kebaabetswe PM, Paxton LA et al. for the TDF2 study group (2012) Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. New England Journal of Medicine 367:423–34

US Food and Drug Administration. Truvada labelling information [Accessed 14 July 2016]

Van Damme L, Corneli A, Ahmed K et al. for the FEM-PrEP study group (2012) Preexposure prophylaxis for HIV infection among African women. New England Journal of Medicine 367: 411–22

Wilton J, Senn H, Sharma M et al. (2015) Pre-exposure prophylaxis for sexually-acquired HIV risk management: a review. HIV/AIDS – Research and Palliative Care 7: 125–36

World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. June 2016

Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

Expert advisers

Dr Monica Desai, Consultant Epidemiologist, Public Health England. Clinical Lecturer, University of York

Dr Kaveh Manavi, Consultant Physician – Lead of HIV Service, University Hospitals Birmingham NHS Foundation Trust

Professor Sheena McCormack, Consultant in HIV/GU Medicine, Chelsea and Westminster Hospital NHS Foundation Trust; Professor of Clinical Epidemiology, Imperial College and Senior Clinical Scientist, Medical Research Council Clinical Trials Unit at UCL

Dr Adrian Palfreeman, Consultant Physician and reader in infection and immunity, University Hospitals Leicester

Dr Leonie Prasad, Consultant in Public Health, Specialised Commissioning; NHS England Midlands & East (East of England)

A draft of this evidence summary was also sent to the Department of Health, Public Health England, NHS England and Gilead Sciences Limited for review.

Declarations of interest

Monica Desai: Co-investigator on the PROUD trial (jointly funded by MRC and PHE; drug provided by Gilead Sciences). Member of BHIVA/BASHH PrEP guidelines working group. Previously Scientific Advisor to the NHS England PrEP policy sub-group for the HIV CRG. Received speaker fees from Janssen.

Kaveh Manavi: Received honoraria from Gilead Sciences, Janssen, MSD, Cepheid for advisory board roles in the past.

Sheena McCormack: Chief investigator on the PROUD trial (Gilead Sciences provided funds and drug free of charge, sponsored by MRC and co-funded by MRC and PHE). Received sponsorship from Gilead for travel and expenses to give talks. Other fees and honoraria from Gilead paid into discretionary account at UCL to enable others to attend international conferences. Authored and co-authored recent publications on PrEP and coordinated the BASHH/BHIVA position statement, co-authored EACS PrEP guidelines and member of BASHH/BHIVA writing group for PrEP guidelines. Member of the Population Council Microbicides Advisory Board. Named in HIV vaccine patent which is no longer maintained.

Adrian Palfreeman: Received sponsorship from Gilead to attend the CROI conference in Boston in February 2016 in line with ABPI guidelines. Member of BHIVA executive committee.

Leonie Prasad: Worked on preparation of documents for the PrEP policy, in particular the evidence review and policy proposition, as a member of the HIV clinical reference group (NHS England). Member of the National Programme of Care Board for Blood and Infection (NHS England), whose oversight includes HIV and has included PrEP. Paid to be interviewed by a market research organisation relating to how HIV services are determined and what we might consider when choosing one antiretroviral drug over another (November 2015).

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

ISBN: 978-1-4731-2114-0