Cabotegravir for preventing HIV-1 in adults and young people [ID6255] Part 1

For Zoom – contains redacted information

Technology appraisal committee C [4th December 2024]

Chair: Stephen O'Brien

Lead team: Alex Cale, Mark Corbett, Stella O'Brien

External assessment group: Warwick Evidence

Technical team: Giacomo De Guisa, Joanna Richardson, Ian Watson

Company: ViiV Healthcare

ACM1 – Preliminary recommendation

Cabotegravir is not recommended, within its marketing authorisation, for pre-exposure prophylaxis (PrEP) alongside safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults and young people who have a high risk of HIV and weigh at least 35 kg.

Key committee rationale

The committee had important concerns about the populations in the clinical evidence and the cost-effectiveness model, and considered that it was not possible to conclude that cabotegravir is a cost-effective option based on the evidence available. It agreed that further analyses were needed to address these uncertainties. So cabotegravir is not recommended for preventing HIV-1.

Cabotegravir for preventing HIV-1 in adults and young people

- ✓ **Background and recap of committee conclusions from 1st meeting**
- ❑ Consultation comments
- ❑ Key issues
- ❑ Equality considerations
- ❑ Summary of cost-effectiveness results

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Background on HIV

- HIV is a retrovirus that infects and destroys immune cells that play a key role in fighting infections
- Estimated 106,890 people were living with HIV in the UK in 2020 and 4,040 newly diagnosed in 2022
- UK government's HIV Action Plan for England (2022 to 2025) aims to achieve zero new HIV transmissions by 2030
- Untreated HIV progresses to late-stage infection, known as acquired immunodeficiency syndrome (AIDS)

Technology details: cabotegravir (Apretude, ViiV Healthcare)

Marketing authorisation	Apretude is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg
Mechanism of action	Second-generation INSTI that inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration
Administration	• Intramuscular injection every 2 months administered by a healthcare professional experienced in the management of HIV PrEP • Daily tablets for approximately 1 month (at least 28 days) can be used as optional oral lead-in to assess tolerability to cabotegravir
Price	• List prices – cabotegravir injections: £1,197.02; oral cabotegravir tablets: £638.57 • Approximate annual cost: £7,820.69 (including 1 month optional oral lead in) • There are existing simple PAS discounts in place for both cabotegravir intramuscular injections and oral cabotegravir tablets due to an existing technology appraisal (TA757)

Abbreviations: CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor

Treatment pathway

= established treatment

= proposed positioning

People at risk of sexually acquired HIV-1 infection

Treatments delivered in Level 3 SHS

- Cabotegravir injections
- Oral TDF/FTC
- Oral TAF/FTC

HIV exposure

HIV acquisition

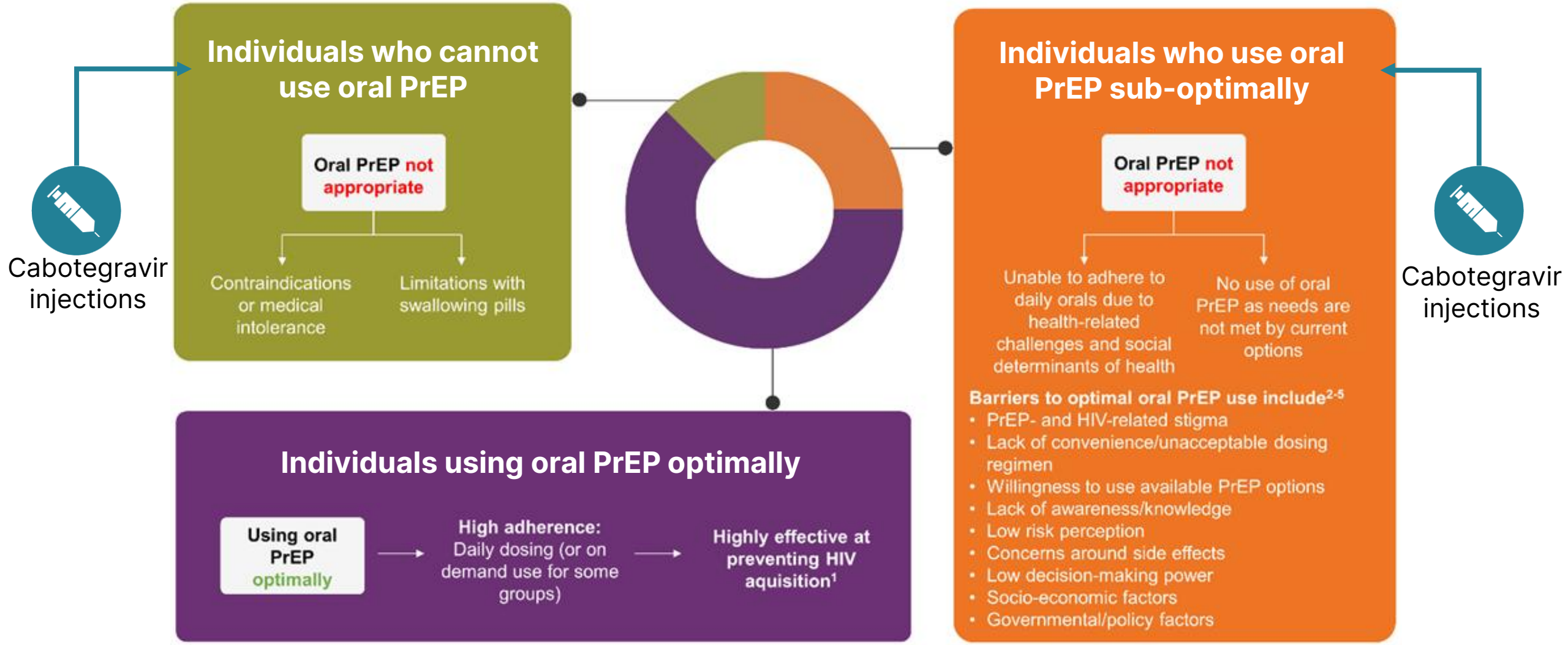
Treatments delivered in secondary care

- Antiretroviral treatment
- Cabotegravir with rilpivirine injections (NICE TA757)

- TDF/FTC and TAF/FTC are both forms of oral PrEP
- The majority of oral PrEP users in the UK will receive TDF/FTC
- TAF/FTC is used for individuals that are intolerant or contraindicated to TDF/FTC (NHS Clinical Commissioning Policy 2023)
- For the pre-exposure prophylaxis of HIV, TAF/FTC is only licensed in MSM

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; SHS, sexual health services; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil/emtricitabine

Populations with PrEP needs



Sources: 1. Sullivan et al, 2023; 2. Calabrese et al, 2020; 3. Coukan et al, 2023; 4. Sidebottom et al, 2018; 5. National AIDS trust

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Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis

= proposed positioning of cabotegravir

ACM1 committee preferred assumptions

Issues discussed	Committee conclusion
Population	Cost-utility analysis using the whole population eligible for cabotegravir, including those who take oral PrEP exactly as prescribed should be presented
Comparators	Both TDF/FTC and no PrEP appropriate comparators
Baseline HIV acquisition	Value of 3.9 per 100 person-years
HIV risk period	Risk period of 10 years
Transition from cabotegravir to TDF/FTC	Uncertainty around exact proportion who should transition to TDF/FTC after stopping cabotegravir
Improved persistence with cabotegravir	Uncertainty around percentage improved persistence applied to cabotegravir compared with TDF/FTC
Adherence to TDF/FTC	Adherence to TDF/FTC lower for CGW compared with MSM and TGW
Starting age of model population	Starting age of 33 years
Cabotegravir administration costs	Administration costs based on 1 hour of clinic time
Cabotegravir injections administration frequency	Administration every 2 months
Disutility associated with living with HIV	Disutility of –0.11 associated with living with HIV

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

Summary of updated company and EAG base case assumptions

Differing assumptions with a large impact on the ICER

Assumption	Company base case	EAG base case
Baseline risk of HIV acquisition	3.9 per 100 person-years*	0.95 per 100 person-years
Transitioning from cabotegravir to oral PrEP	[redacted] of individuals transition from cabotegravir to oral PrEP†	No transitioning from cabotegravir to oral PrEP†
Persistence to cabotegravir	20% improved persistence for cabotegravir over oral PrEP†	Persistence to cabotegravir equal to oral TDF/FTC†
Duration of risk period	5 years	10 years*
Disutility for HIV	–0.11*	–0.05
Discontinuation rate correction	Discontinuation rate 'error' corrected	Unchanged

*aligns with ACM1 committee conclusion

†committee concluded at ACM1 that there is uncertainty around the assumption

Note: Baseline risk of 3.9 per 100 PY was the EAG's previous preferred assumption for its original base case at ACM1 before draft guidance consultation. 0.95 per 100 PY was suggested in the UKHSA's response to draft guidance.

See appendix – Differing assumptions with a small impact on the ICER

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Abbreviations: ACM, appraisal committee meeting; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; PY, person-yearsTDF/FTC, tenofovir disoproxil/emtricitabine; UKHSA, UK Health Security Agency

Cabotegravir for preventing HIV-1 in adults and young people

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Summary of consultation responses

Commenters

- British HIV Association (professional organisation)
- UK Health Security Agency (professional organisation)
- National AIDS trust (community organisation)
- ViiV Healthcare (the company)
- 2 clinical experts
- 7 web comments

Comment themes

- Unmet need
- Individuals who use oral PrEP sub-optimally
- Clinical trial populations
- Duration of HIV risk period
- Baseline risk of HIV acquisition
- Improved persistence with cabotegravir injections
- Adherence to TDF/FTC
- Cabotegravir administration costs
- Starting age of modelled population

See appendix for detailed consultation responses

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

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Equality considerations – ACM1

- HIV disproportionately affects: people of Black African family background; people of certain sexual orientation such as gay or bisexual men
- Key populations most at risk of HIV acquisition may be reluctant to engage in healthcare systems or to access sexual health services. Cultural concerns or stigma may exacerbate health inequity.
- Long-acting injections may not suit people who cannot easily access or schedule the necessary clinic appointments
- Long-acting injections may benefit some young people who struggle with managing oral therapies
- Acknowledged inequity of access to PrEP in the UK for cis-gender women
- Eligibility for key cabotegravir trials excluded current or planned pregnancy or breastfeeding status

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis

Equality considerations

Equality considerations raised during consultation

- If oral PrEP remains the sole option for women, this will reduce its acceptability and uptake among the most vulnerable, potentially leading to preventable new HIV transmissions
- For women with a PrEP need, the committee should consider the advantages of offering multiple administration routes in contraception and how these benefits could be applied to PrEP
- TAF/FTC is not licensed in CGW, creating inequity for women with contraindications to TDF/FTC
- UKHSA 2023 - only 40.9% of heterosexual and bisexual women with a PrEP need, initiated or continued PrEP
- Deepening inequality in HIV outcomes, with increasing rates being seen in key populations, such as Black women, whose needs are not currently being met with available oral PrEP regimens
    - Access to cabotegravir for PrEP is important to improve equity of access and to begin to address these disparities in outcomes for key populations.

What are the committee's issues on the equalities issues raised?
Are there any further equality considerations the committee should consider?

Abbreviations: ACM, appraisal committee meeting; CGW, cisgender women; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TAF/FTC, tenofovir alafenamide/emtricitabine; UKHSA, UK Health Security Agency

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Key issues for discussion

Key issue	Questions for committee	ICER impact
Appraisal population	• Does the company's analysis reflect the committee's preferred population?	Unknown
Baseline risk of HIV acquisition	• What is the most appropriate baseline risk of HIV acquisition considering new UKHSA data?	Very large
Duration of HIV risk period	• What is the most appropriate at-risk period?	Large
Transition from cabotegravir to TDF/FTC	• Is it appropriate to allow participants to transition to TDF/FTC after discontinuing cabotegravir? • Does the company's scenario analyses impact the committee's decision?	Large
Improved persistence with cabotegravir	• Is it plausible to assume that cabotegravir injections will improve persistence compared to oral PrEP? • Does the company's new real-world evidence and scenario analyses impact the committee's decision?	Large
Discontinuation rate correction	• What is the committee's preferred methods for applying discontinuation rates in the model?	Large

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine; UKHSA, UK Health Security Agency

Other issues

Other issue	Questions for committee	ICER impact
Starting age of participants	• What is the most appropriate staring age of the model cohort considering new UKHSA data?	Small 
Cabotegravir administration costs	• What is an appropriate amount of time to assume for cabotegravir injections to be administered?	Small 

Slides on other issues can be found in the supplementary appendix:

- Starting age of participants
- Cabotegravir administration costs

Abbreviations: UKHSA, UK Health Security Agency

Key issue: Appraisal population

Background

- During ACM1, committee noted that the clinical trial populations would have included people who took oral PrEP optimally and that it was difficult to define the subpopulation who take oral PrEP sub-optimally
- Committee concluded that a CUA of the whole population eligible for cabotegravir should be presented

Company

- Agree that individuals that take oral PrEP sub-optimally may be difficult to identify in practice
- People who take oral PrEP optimally have already been captured in the original submission
- Clinical evidence represents population who take oral PrEP as prescribed and those who do not
- Clinical trials inclusion criteria were aligned with cabotegravir MA and the population were a mix of individuals with optimal and suboptimal adherence
- All the trial data was used in the health economic model to compare cabotegravir to TDF/FTC and assumed to lead to a conservative cost-effectiveness estimate for people with the greatest unmet need
- Clinical SLR included studies with placebo arms or no PrEP groups which were included in the ITC
- Effectiveness of cabotegravir vs no PrEP estimated in ITC is generalisable to the population who cannot take oral PrEP and therefore the cost-effectiveness results are applicable to this population

EAG comments

- Agree that the population modelled by the company originally reflects the committee's preferred population
- However this has implications for the baseline HIV incidence rate used in economic model [see next slide]

Does the company's analysis reflect the committee's preferred population?

Abbreviations: ACM, appraisal committee meeting; CUA, cost utility analysis; ITC, indirect treatment comparison; MA, marketing authorisation; PrEP, pre-exposure prophylaxis; SLR, systematic literature review; TDF/FTC, tenofovir disoproxil/emtricitabine

Key issue: Baseline risk of HIV acquisition

Background

- Consultation comments from UKHSA suggest using lower baseline risk of HIV acquisition (EAG agrees)
- During ACM1, the committee concluded a baseline risk of 3.9 per 100 PY was appropriate

UKHSA comments

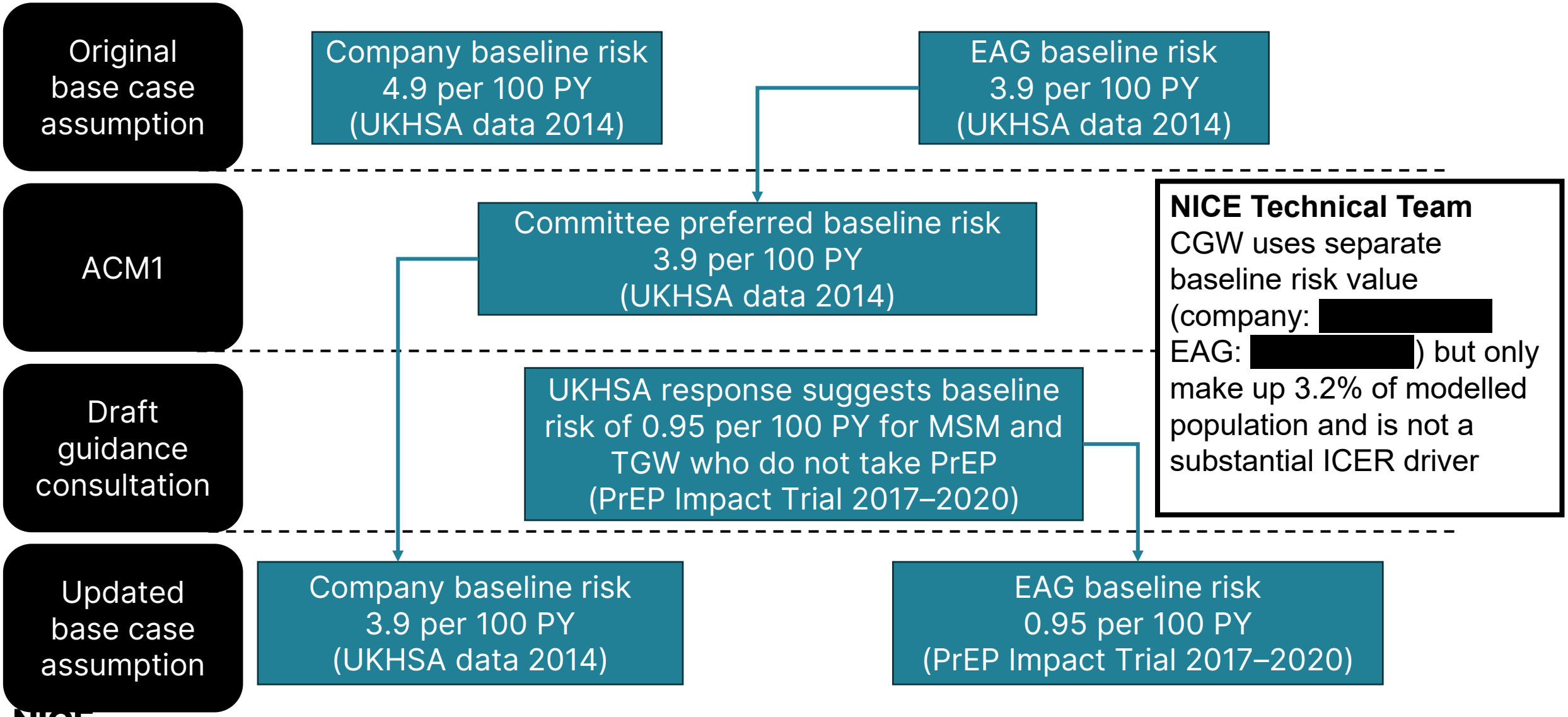
- Company's and EAG's preferred baseline risk values for MSM and trans women are based on UKHSA data from 2014 estimating HIV incidence amongst MSM attending SHS
- UKHSA data estimates that HIV incidence amongst MSM declined 77% between 2014 and 2022
- PrEP Impact Trial assessed HIV incidence amongst attendees at sexual health services in England between 2017 and 2020 and provides a robust estimate of current incidence rates amongst MSM
- UKHSA recommend a baseline risk of 0.95 per 100 PY for MSM and TGW not taking oral PrEP and 0.13 per 100 PY for MSM and TGW taking oral PrEP

EAG comments

- Re-defined population has implications for the baseline HIV incidence rate used in economic model
- Previous estimate that reflects the previously defined narrower population and used 2014 data that reported HIV incidence in MSM with recent rectal bacterial STI
- The original estimate (3.9 per 100 PY) is not appropriate for the whole population eligible for cabotegravir
- Agree with UKHSA's baseline risk of 0.95 per 100 PY for whole population eligible for cabotegravir

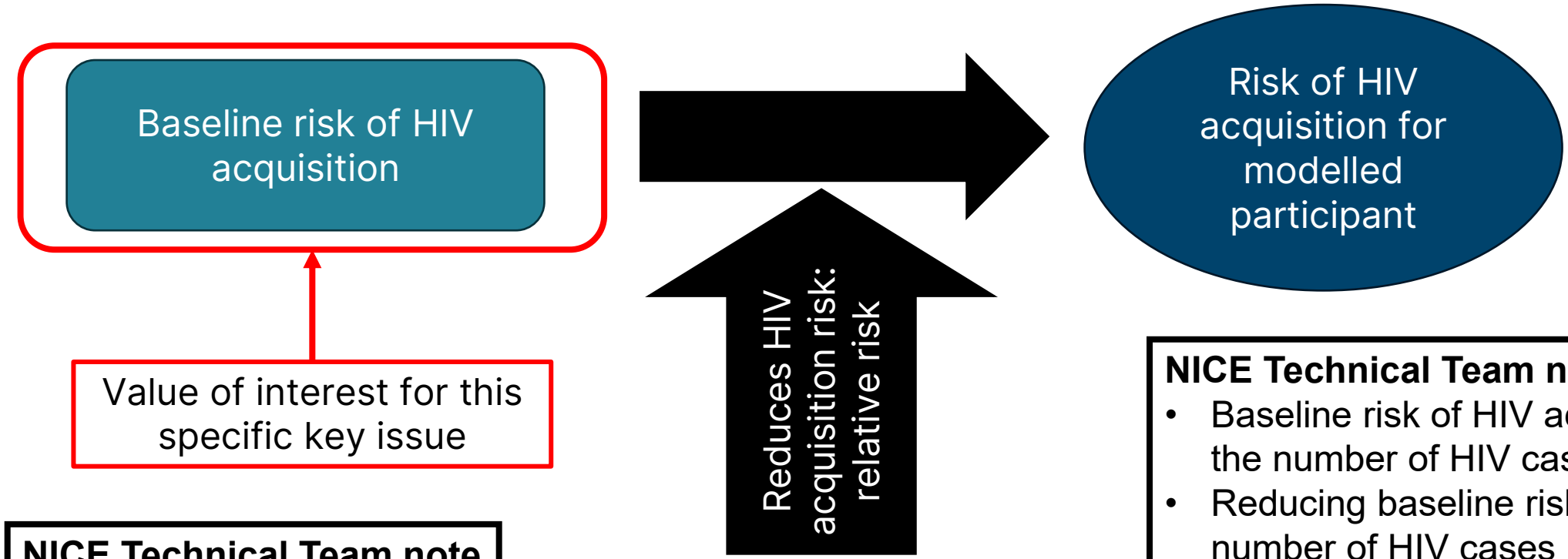
Abbreviations: ACM, appraisal committee meeting; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; PY, person years; SHS, sexual health services; STI, sexually transmitted infection; TDF/FTC, tenofovir disoproxil/emtricitabine; TGW, transgender women; UKHSA, UK Health Security Agency

Key issue: Baseline risk of HIV acquisition – MSM and TGW



Abbreviations: ACM, appraisal committee meeting; CGW, cisgender women; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; PY, person-years; TGW, transgender women; UKHSA, UK Health Security Agency

Key issue: Baseline risk of HIV acquisition



NICE Technical Team note

- This is a highly simplified representation of part of the economic model

NICE Technical Team note

- Baseline risk of HIV acquisition impacts the number of HIV cases in the population
- Reducing baseline risk reduces the number of HIV cases in the population
- This reduces the incremental QALY gain cabotegravir provides and increases the ICER
- Baseline risk is the largest ICER driver

What is the most appropriate baseline risk of HIV acquisition?
In practice does the baseline risk of HIV acquisition differ across specific population groups (e.g. people having different comparators)?

Abbreviations: ACM, appraisal committee meeting; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; PY, person-years; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil/emtricitabine; UKHSA, UK Health Security Agency

Key issues: Duration of HIV risk period and associated costs

Background

- Company and EAG disagree on the appropriate at-risk period for HIV acquisition (5 years vs 10 years)
- In practice, a person's level of HIV risk will change throughout their lifetime and that PrEP is mostly used over multiple short-term periods. Using a single risk period of 5 or 10 years is a simplification for modelling.
- During ACM1, the committee concluded an at-risk period for HIV acquisition of 10 years was appropriate

Company

- Still believe an at-risk period of 5 years is appropriate
- RWE on persistence to oral PrEP demonstrates a high rate of discontinuation (over 40% at 12 months)
- Clinical experts at ACM1 supported a HIV risk period of 5 years
- Additional scenario analyses exploring a 10-year risk period were conducted

EAG comments

- Retains previous base case assumption of a 10-year risk period

What is the most appropriate at-risk period?

Abbreviations: ACM, appraisal committee meeting; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; RWE, real-world evidence

Key issue: Transition from cabotegravir to TDF/FTC

Background

- Company and EAG disagree on whether modelled participants should transition to TDF/FTC (oral PrEP) after discontinuation of cabotegravir (allowing transition vs not allowing transition)
- ACM1 conclusion: Uncertain on percentage that should transition to TDF/FTC after stopping cabotegravir

Company

- As the full population (people who take oral PrEP as prescribed and those who do not) is being considered, it is reasonable to assume that [redacted] of people will take TDF/FTC after discontinuation of cabotegravir
- Maintain that this is in line with cabotegravir SmPC recommendation
- Scenario analyses conducted assuming [redacted] and [redacted] of people transition from cabotegravir to TDF/FTC and cabotegravir dominated TDF/FTC in both scenarios
- No transitioning was assumed when comparing cabotegravir with no PrEP

EAG comments

- Not logical for people in cabotegravir arm to transition to oral PrEP if it is not appropriate for them
- Company does not make a similar assumption for people in the oral TDF/FTC arm transitioning to cabotegravir, which biases ICERs in favour of cabotegravir
- EAG still prefers no transitioning from cabotegravir to TDF/FTC

Is it appropriate to allow participants to transition to TDF/FTC after discontinuing cabotegravir? Does the company's scenario analyses impact the committee's decision?

Abbreviations: ACM, appraisal committee meeting; ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine; SmPC, summary of product characteristics

Key issue: Improved persistence with cabotegravir

Background

- Company and EAG disagree on whether persistence with cabotegravir improves relative to TDF/FTC (20% improvement vs no improvement)
- ACM1 conclusion: Uncertain on percentage improved persistence that should be applied to cabotegravir
- **Persistence** refers to the willingness to continue taking a prescribed treatment for a given length of time

Company

- Company maintains that persistence and adherence are distinct outcomes
- A 20% persistence improvement translates into a proportion of 84.2% and 68.9% of individuals remaining on cabotegravir at 6 and 12 months respectively
- This is consistent with findings from new real-world evidence from 15 clinics in the United States with cabotegravir retention being 84.8% (95% CI 80.9−88.9%) for the first 6 months
- For scenario analyses assuming 10% improvement, cabotegravir dominated TDF/FTC and no PrEP

EAG comments

- Lack of evidence on the company's base case assumption of improved persistence of cabotegravir compared to oral PrEP
- EAG considers no relative improvement in persistence to cabotegravir compared to oral PrEP

Will cabotegravir injections improve persistence compared to oral PrEP and to what degree?
Does the company's new real-world evidence and scenario analyses impact the committee's decision?

Abbreviations: ACM, appraisal committee meeting; ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

Key issue: Discontinuation rate correction

Background

- Company identified an error in the implementation of discontinuation rates in its cost effectiveness model, but EAG do not believe it is an error that needs correcting

Company

- Discontinuation rates for oral PrEP and cabotegravir (estimated from data to 6 months) were erroneously applied for 5 monthly cycles instead of 6
- This implementation error has been corrected in the updated base-case analysis

EAG comments

- Company's claim that discontinuation rates were applied for 5 monthly cycles is factually inaccurate
- Discontinuation rates were applied for 6 monthly cycles in the previous implementation and 7 monthly cycles in the current implementation
- Cycle begins from Month 1 and not 0, so the cohort would have spent 6 months in the various health states at the end of the 6th cycle

What is the committee's preferred method for applying discontinuation rates in the model?

Abbreviations: PrEP, pre-exposure prophylaxis

Key issues

Key issue	ICER impact	Slide
Appraisal population	Unknown	17
Baseline risk of HIV acquisition	Very large	18
Duration of HIV risk period and associated costs	Large	21
Transition from cabotegravir to TDF/FTC	Large	22
Improved persistence to cabotegravir	Large	23
Discontinuation rate correction	Large	24

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

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Summary of updated company and EAG base case assumptions

Differing assumptions with a large impact on the ICER

Assumption	Company base case	EAG base case
Baseline risk of HIV acquisition	3.9 per 100 person-years*	0.95 per 100 person-years
Transitioning from cabotegravir to oral PrEP	[redacted] of individuals transition from cabotegravir to oral PrEP†	No transitioning from cabotegravir to oral PrEP†
Persistence to cabotegravir	20% improved persistence for cabotegravir over oral PrEP†	Persistence to cabotegravir equal to oral TDF/FTC†
Duration of risk period	5 years	10 years*
Disutility for HIV	–0.11*	–0.05
Discontinuation rate correction	Discontinuation rate 'error' corrected	Unchanged

*aligns with ACM1 committee conclusion

†committee concluded at ACM1 that there is uncertainty around the assumption

Note: Baseline risk of 3.9 per 100 PY was the EAG's previous preferred assumption for its original base case at ACM1 before draft guidance consultation. 0.95 per 100 PY was suggested in the UKHSA's response to draft guidance.

See appendix – Differing assumptions with a small impact on the ICER

Abbreviations: ACM, appraisal committee meeting; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; PY, person-yearsTDF/FTC, tenofovir disoproxil/emtricitabine; UKHSA, UK Health Security Agency

Summary of updated company and EAG base cases

Exact results are reported in part 2

- Cost-effectiveness results are confidential because there is a confidential PAS for cabotegravir, and TDF/FTC and TAF/FTC have confidential MPSC prices
- Cost-effectiveness analyses include company and EAG base cases, company deterministic scenario analyses and the impact of individual EAG assumptions on the company base case

Company base case

- Cabotegravir is less costly and generated more QALYs than TDF/FTC
- ICER for cabotegravir remains dominant over TDF/FTC
- ICER for cabotegravir remains dominant over no PrEP
- Probabilistic results similar to deterministic results

EAG base case

- Cabotegravir is more costly and generated more QALYs than TDF/FTC
- ICER for cabotegravir vs TDF/FTC remains considerably higher than £30,000 per QALY gained
- ICER for cabotegravir vs no PrEP is higher than £30,000 per QALY gained
- Probabilistic results similar to deterministic results

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Abbreviations: ICER, incremental cost-effectiveness ratio; MPSC, Medicines Procurement and Supply Chain; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil/emtricitabine

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Supplementary appendix

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Key clinical trials

Clinical trial results

HPTN 083* - trial conducted in Latin American and SE Asian countries, the US and South Africa in MSM and TGW

	Cabotegravir (N=2,280)	Daily oral TDF/FTC (N=2,281)
Number of HIV acquisitions	13	39
Person-years	3,211	3,193
Incidence rate/100 PY	0.40 [redacted]	1.22 [redacted]
Unadjusted HR; superiority p value	[redacted]	
Bias-adjusted HR; superiority p value	0.34 (0.18, 0.62); [redacted]	

HPTN 084* - conducted in sub-Saharan African countries in CGW

	Cabotegravir (N=1,614)	Daily oral TDF/FTC (N=1,610)
Number of HIV acquisitions	4	36
Person-years	[redacted]	[redacted]
Incidence rate/100 PY	0.20 [redacted]	1.85 [redacted]
Unadjusted HR; superiority p value	0.11 (0.04, 0.31); p<0.0001	
Bias-adjusted HR; superiority p value	0.12 (0.05, 0.31); p<0.0001	

*Analysis from Steps 1 and 2 for the clinical trials (153 weeks)

Abbreviations: CGW, cisgender women; HIV, human immunodeficiency virus; HR, hazard ratio; MSM, men who have sex with men; PY, person-years; SE, South-East; TDF/FTC, tenofovir disoproxil/emtricitabine TGW, transgender women

Results of indirect treatment comparison

Parameter	Log Relative Risk		% Effectiveness		
	Mean	SD	Mean	2.5% CrI	97.5% CrI
Cabotegravir versus TDF/FTC (HPTN 083 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir versus TDF/FTC (HPTN 084 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TDF/FTC versus no PrEP (HPTN 083 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TDF/FTC versus no PrEP (HPTN 084 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir versus no PrEP (HPTN 083 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir versus no PrEP (HPTN 084 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

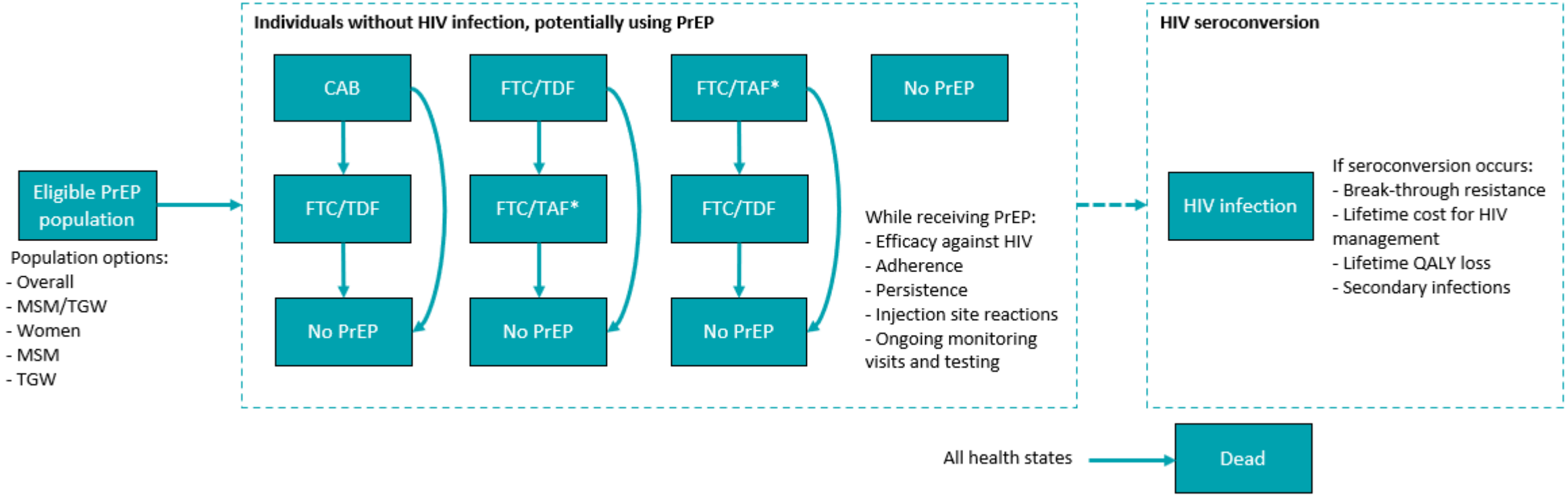
Company

- The predicted effectiveness of cabotegravir versus TDF/FTC is [redacted] for the CGW population (HPTN 084 trial) ([redacted]) versus the MSM and TGW population (HPTN 083 trial) ([redacted])
- Corresponds with lower adherence to TDF/FTC observed in HPTN 084 (56%), compared with HPTN 083 (86%)
- When combining relative effectiveness of cabotegravir versus TDF/FTC and adherence level to TDF/FTC, the estimated effectiveness of cabotegravir versus no PrEP is [redacted] for the CGW population (HPTN 084 trial) and [redacted] for the MSM and TGW population (HPTN 083 trial)

Abbreviations: CGW, cisgender women; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine; TGW, transgender women

Company's model structure

Model structure



* FTC/TAF is only available for MSM and TGW subpopulations.

Abbreviations: CAB, cabotegravir; CGW, cisgender women; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; FTC/ TAF, tenofovir alafenamide/emtricitabine; FTC/TDF, tenofovir disoproxil/emtricitabine; TGW, transgender women

Consultation responses – unmet need

- UKHSA 2023 data shows a rise in HIV rates within the UK (6008 new HIV diagnoses, an increase of 51% from 2022)
- A small proportion of individuals struggle to take daily tablets due to adherence issues or privacy concerns and some are unable to tolerate oral PrEP due to side effects or may have medical contraindications, representing a clear unmet need
- Choice and patient autonomy is paramount in order to support user acceptance and drive overall increases in uptake of PrEP
    - Only offering oral PrEP will hinder efforts to increase acceptability, particularly amongst harder to reach, non-GBMSM populations
- There is a challenging gap in HIV prophylaxis for people whom TDF/FTC or TAF/FTC is contraindicated
- It is essential that cabotegravir is made available to help ensure the UK government meets its the HIV Action Plan target of ending new HIV cases by 2030

Link to – Summary of consultation responses

Abbreviations: GBMSM, gay, bisexual and men who have sex with men; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF/FTC, tenofovir disoproxil/emtricitabine; UKHSA, UK Health Security Agency

Consultation responses – individuals who use oral PrEP sub-optimally

- Clinicians who specialise in sexual health and HIV prevention have considerable experience in identifying and supporting those who struggle to take oral PrEP
- Clinicians are also experienced in having sensitive discussions that would identify those who have stigma-related, psychology, socio-economic or personal / relationship reasons that would make injectable PrEP a preferrable option to oral PrEP
- Engagement in clinical care is a surrogate marker for persistence, so clinicians are well placed to identify individuals in whom alternative PrEP options would be of benefit
- It is highly unlikely that individuals who currently take oral PrEP as prescribed will enter the subpopulation of 'sub-optimal use' in order to access cabotegravir
    - The same concerns were raised with the introduction of injectable antiretroviral therapy but currently, less than 2% of people with HIV on antiretroviral therapy have switched to injectables
    - Recently updated PrEP guidelines (currently out for consultation) offer easier options for PrEP dosing, which should support continued adherence to oral PrEP for those who take it exactly as prescribed

Link to – Summary of consultation responses

NICE

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis

Consultation responses – clinical trial populations and duration of HIV risk period

Clinical trial populations

- Whilst it was not a specific inclusion criterion, it is clear from the adherence data that people who struggle to take oral PrEP were included in the clinical trials
- Clinical trial results are generalisable to the UK context, as the populations face similar risks and barriers

Duration of HIV risk period

- 10-year at-risk period for HIV acquisition used in the economic model does not align with clinical practice and likely overestimates the duration PrEP use and the associated costs for most individuals
- It is acknowledged that HIV risk can fluctuate over time due to changes in personal circumstances such as relationship status or behaviour
- A 5-year risk period is more accurate and closer to clinical experience

Link to – Summary of consultation responses

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis

Consultation responses – baseline risk of HIV acquisition

- Company's and EAG's preferred values for MSM and trans women are based on UKHSA data from 2014 estimating HIV incidence amongst MSM attending sexual health services
    - Modelling evidence calibrated to UKHSA data estimates that HIV incidence amongst MSM declined 77% between 2014 and 2022 (Cambiano 2024)
- PrEP Impact Trial assessed HIV incidence amongst attendees at sexual health services in England between 2017 and 2020 and provides a robust estimate of current incidence rates amongst MSM attending SHSs which can be disaggregated by PrEP usage
- UKHSA recommend a baseline risk of 0.95 per 100 PY for MSM and TGW not taking oral PrEP and 0.13 per 100 PY for MSM and TGW taking oral PrEP
- Additional concerns about the company's preferred estimates, which use trial data from sub-Saharan Africa to approximate risk amongst women living in the UK as epidemiology, as healthcare delivery and access to services vary markedly between these contexts
- Most credible estimate of incidence in eligible cisgender women that UKHSA is aware of is from a study of SHS attendees between 2009-2013 (Aghaizu, 2018)

Link to – Summary of consultation responses

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; PY, person-years; SHS, sexual health services; TGW, transgender women; UKHSA, UK Health Security Agency

Consultation responses – improved persistence with cabotegravir injections

- It is crucial for the committee to place greater emphasis on enhancing persistence among individuals who struggle to adhere to or tolerate daily oral PrEP because these people represent the communities most likely to seek cabotegravir in real-world settings
- Assuming persistence with cabotegravir will be equal to oral PrEP fails to take into account the increased acceptability of a novel injectable form of PrEP in cabotegravir and ignores the acceptability impact of providing greater choice of PrEP options
- Individuals who are able to access cabotegravir injectable PrEP will be taking a form of PrEP that is more suited to them so persistence will be better
- Cabotegravir will improve non-stigma related adherence to oral PrEP by reducing errors in daily pill-taking
- There is uncertainty around the percentage improvement of persistence but it should not be underestimated

Link to – Summary of consultation responses

Abbreviations: PrEP, pre-exposure prophylaxis

Consultation responses – adherence to TDF/FTC

- Data from 56 Dean Street, a large sexual health service within Chelsea and Westminster NHS Trust, shows 24% of individuals with newly diagnosed HIV had evidence of PrEP exposure, with adherence challenges the likely reason for PrEP failure
- Agree with committee assumption that adherence to TDF/FTC lower for cisgender women compared with men who have sex with men and transgender women
- UK Government's PrEP Roadmap (February 2024) notes that women are much less likely to continue using HIV PrEP than gay, bisexual and other men who have sex with men

Link to – Summary of consultation responses

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine

Consultation responses – cabotegravir administration costs

- Appointments to administer of cabotegravir injections are likely to be considerably shorter than 1 hour clinic time
- Services who already have some experience of providing cabotegravir PrEP through compassionate access suggest that appointments take between 20 to 45 minutes
- Clinical experience of providing injectable therapy for people living with HIV suggests this can be managed in a nurse-led clinic with a 30-minute appointment
- A 30-minute appointment is likely to be even more appropriate once an individual is established on injectable cabotegravir PrEP, especially if the individual has already undergone online STI testing
- Administration costs for cabotegravir injections should be based on less than 1 hour clinic time

Link to – Summary of consultation responses

Abbreviations: PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection

Consultation responses – starting age of modelled population

- UKHSA data continues to show that the modal age group of populations starting or continuing oral PrEP in 2023 is 25 to 34 (UKHSA, 2024).
- Median age for current PrEP users will be older than the age at which people initiate PrEP – so the age of PrEP initiation may be at the lower end of this age band (closer to 25 years)
- Individuals are most likely to have multiple sexual partners between the ages of 16 and 24
    - Data on heterosexual sex from the National Survey of Sexual Attitudes and Lifestyles shows that men and women are most likely to report having at least one new sexual partner in the last year, and more than two sexual partners with whom no condom was used in the last year, between the ages of 16 and 24 (Mercer, 2013)

Link to – Summary of consultation responses

Abbreviations: PrEP, pre-exposure prophylaxis; UKHSA, UK Health Security Agency

Other issue: Starting age of participants

Background

- Company and EAG disagree on appropriate starting age of model cohort (31.5 and 29 years vs 33 years)
- During ACM1, the committee concluded a starting age of 33 years was appropriate for the model cohort

Company

- New UKHSA data up to 2023 shows median age of those accessing oral PrEP for both MSM and TGW, and CGW within the groups aged 25–34
- Company estimates the median age to be 34.0 years MSM and TGW, and 31.5 years for CGW (assuming uniform age distribution)
- The midpoint of the 5-year period of elevated risk should correspond to the cohort's median age, so starting age for these cohorts in the model should be 2.5 years younger
- Similarly, if the duration of the at-risk period is changed to 10 years, the starting age should be updated in the model to be 5 years younger than the estimated median

EAG comments

- Retains previous base case assumption of model participant starting age of 33 years

What is the most appropriate staring age of the model cohort considering new UKHSA data?

Abbreviations: CGW, cisgender women; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TGW, transgender women; UKHSA, United Kingdom Health Security Agency

Other issue: Cabotegravir administration costs

Background

- Company and EAG disagree on costs associated with administering cabotegravir injections (EAG's higher)
- During ACM1, the committee concluded cabotegravir administration costs should be based on 1 hour of clinic time

Company

- Maintains that administration of cabotegravir requires two 30-minute initiation injection appointments, with 20-minute appointments for subsequent injections
- Company base case includes the cost of 30 minutes of a medical consultant's time for subsequent injection visits in addition to the 20 minutes of nurse's injection administration time
- EAG's preferred assumption implies that subsequent appointments will take 90 minutes: 20 minutes of Band 5 nurse time for observation, 40 minutes of clinical activity and 30 minutes of medical consultant time

EAG comments

- Company's claim is factually inaccurate, EAG's analysis accounted for an hour of administration which includes 20 mins of a Band 5 Nurse time for observation and 40 mins of clinical activity
- Updated base case to include 1 hour of clinical activity for the first two injection visits, with subsequent injection visits are assumed to incur an administration time of 30 mins

What is an appropriate amount of time to assume for cabotegravir injections to be administered?

Company changes to model parameters (1/3)

Updated model parameters reflecting 2024 UKHSA report

Model parameter	Previous base case (UKSHA 2023)	Updated base case (UKHSA 2024)
% MSM and TGW	96.86%	96.82%
% CGW	3.14%	3.18%
Starting age MSM and TGW	31 years	31.5 years
Starting age CGW	29 years	29 years

Company

- 2024 UKHSA report on HIV testing, PrEP, new HIV diagnoses and care outcomes for people accessing HIV services has been released since original submission
- Latest data release shows that there has been an increase in HIV acquisitions first diagnosed in England across every population between 2022 and 2023
- Based on the latest data release, the calculated median age was 34.0 years for MSM and TGW, and 31.5 years for CGW
- Starting age of the model was adjusted so that the median age aligns with the of the duration of the period of elevated risk

Abbreviations: CGW, cisgender women; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine TGW, transgender women; UKHSA, UK Health Security Agency

Company changes to model parameters (2/3)

Updated model parameters reflecting corrected errors in the ITC

* Percentage effectiveness

	Before correction (original analysis)	After correction
HPTN 083		
TDF/FTC vs. no PrEP	[redacted]	[redacted]
Cabotegravir vs. no PrEP (95% CI)	91.10%* (82.87%–95.95%)	[redacted]
HPTN 084		
TDF/FTC vs. no PrEP	[redacted]	[redacted]
Cabotegravir vs. no PrEP (95% CI)	92.52%* (83.02%–97.38%)	[redacted]
Baseline HIV incidence	[redacted]	[redacted]

Company

- Error in the extraction of data from the Partners PrEP study that informed the ITC was identified and corrected
- Further refinement of the ITC to address EAG concerns that the original ITC had not accounted for measurement error in adherence levels in the meta-regression of treatment effect on adherence to oral PrEP

EAG comments

- Company's correction of this error has minimal impact on the cost-effectiveness estimates
- EAG welcomes the company's revision of its base-case to account for uncertainty in the adherence measures

Abbreviations: HIV, human immunodeficiency virus; HR, hazard ratio; ITC, indirect treatment comparison'; PrEP, pre-exposure prophylaxis; PY, person-years; TDF/FTC, tenofovir disoproxil/emtricitabine

Company changes to model parameters (3/3)

Updated model parameters reflecting corrected errors for renal function tests

Company

- Error in the implementation of health care resource use associated with renal function tests for TDF/FTC and cabotegravir was identified
- In the original economic model, tests of kidney function (eGFR, urinalysis, serum creatinine) were applied at baseline (year 1) for both TDF/FTC and cabotegravir
- Regular monitoring of renal function for individuals on TDF/FTC due to associated risks
- SmPC for cabotegravir does not recommend testing of kidney function, as there is no link between cabotegravir and renal impairment, so monitoring costs were removed for the cabotegravir arm in the model

EAG comments

- Cannot verify the company's claim about requirements for renal function tests in PrEP users on TDF/FTC and cabotegravir
- However, EAG has included the updated frequency of renal function tests in its base case

Abbreviations: eGFR, estimated glomerular filtration rate; SmPC, summary of product characteristics; TDF/FTC, tenofovir disoproxil/emtricitabine

Summary of company and EAG base case assumptions

Differing assumptions with a small impact on the ICER

Assumption	Company base case	EAG base case
Adherence to TDF/FTC	Adherence for CGW is lower than TGW and MSM*	Adherence for CGW is equal to TGW and MSM
Per cycle application of injection site reaction (ISR) costs & disutility	No disutility value applied for ISR	Disutility value of –0.015 applied per cycle for ISR
Cabotegravir administration costs	Based on two 30-minute initiation appointments and 20-minute subsequent appointments	Based on an hour of clinic activity*
Cabotegravir dosing schedule	Every 2 months*	Every 8 weeks
Cabotegravir acquisition costs to account for change in risk patterns	No increase	Increased by 5%
Starting age of model cohort	31 years for MSM and TGW; 29 years for CGW	33 years*

*aligns with ACM1 committee conclusion

Link to – Differing assumptions with a large impact on the ICER

Abbreviations: CGW, cisgender women; ISR, injection site reaction; MSM, men who have sex with men; TDF/FTC, tenofovir disoproxil/emtricitabine; TGW, transgender women

Company's model overview

Technology affects **QALYs** by:

- Assumption of improved persistence to cabotegravir
- Transition to TDF/FTC following discontinuation from cabotegravir
- Duration of assumed aggregate risk period
- Adherence to PrEP regimens

Technology affects **costs** by:

- Drug acquisition and administration costs
- Cabotegravir administration frequency
- Adverse events costs
- HIV management costs

Assumptions with greatest ICER effect:

- Baseline HIV incidence
- Assumed improved persistence to cabotegravir
- Transition to TDF/FTC following discontinuation from cabotegravir
- Duration of assumed aggregate risk period
- Frequency of administration of cabotegravir
- Increased cabotegravir acquisition costs due to implications of restarting cabotegravir over the lifetime of the cohort

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil/emtricitabine