Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

Appraisal Committee meeting 2 – 4 December 2024

1. **Community group submission from National AIDS Trust**

2. **Comments on the Draft Guidance from ViiV Healthcare**

3. **Consultee and commentator comments on the Draft Guidance** from:
   a. National AIDS Trust
   b. British Association for Sexual Health and HIV
   c. British HIV Association
   d. UK Health Security Agency

4. **Comments on the Draft Guidance from experts:**
   a. Dr Michael Brady, Consultant in HIV and Sexual Health – clinical expert, nominated by ViiV healthcare
   b. Dr Rachael Jones, Consultant Physician – clinical expert, nominated by NHS England Specialised Commissioning

5. **Comments on the Draft Guidance received through the NICE website**

6. **External Assessment Group critique of company comments on the Draft Guidance**

7. **External Assessment Group critique of company comments on the Draft Guidance – Additional evidence**

Appraisal Committee meeting 3 – 8 July 2025

8. **Company additional information provided post-appraisal committee meeting 2:**
   a. Company additional evidence submission
   b. Company additional evidence submission addendum

9. **Patient group, professional group and NHS organisation additional evidence submissions** from:
   a. British HIV association
   b. National Aids Trust

c. UK Health Security Agency

10. Expert personal perspectives from:
Rachael Jones– clinical expert, nominated by NHS England

11. External Assessment Group report on additional evidence post FAC

12. External Assessment Report – factual accuracy check

13. Decision Support Unit report on additional evidence post FAC

14. DSU report – factual accuracy check

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Community Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for community submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable

We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.

Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	National AIDS Trust (NAT)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	National AIDS Trust (NAT) is the UK's HIV rights charity. We work to stop HIV from standing in the way of health, dignity and equality, and to end new HIV transmissions. Our expertise, research and advocacy secure lasting change to the lives of people living with and at risk of HIV. NAT receives its funds through trusts and foundations, individual giving, corporate support and pharmaceutical companies. We limit our statutory funding and funding we receive from pharmaceutical companies to ensure that we remain independent and maximise our effectiveness.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Funding received from ViiV (since Jan 2023) 17 March 2023 - £20,000 core funding 30 June 2023 - £69,663 HIV Prevention 1 September 2023 - £49,000 HIV Outcomes Funding received from Gilead: (since Jan 2023) £8,010 3rd and final tranche stigma project £650 speaker fee £49,000 HIV Outcomes £17,358.50 Gilead fellowship

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of people at risk of sexually acquiring HIV-1 and carers (if applicable) to include in your submission?	**1. Not PrEPared report** The Not PrEPared report created by NAT, Terrence Higgins Trust (THT) PrEPster, Sophia Forum, and the One Voice Network collected data from local authority sexual health commissioners, clinic staff, PrEP users who had experienced issues accessing PrEP and those who sought to access PrEP but were unsuccessful.[1] The report provided the results of three surveys: - PrEP service users and those seeking to use PrEP - Clinicians involved in providing PrEP - Sexual health service commissioners and providers across the UK **2. Community Advisory Board** The National AIDS Trust has a Community Advisory Group which is a group of people living with HIV that provides input to our work, helping us to prioritise our work and making sure that we stay relevant. Members of our Community Advisory Group come from a wide range of backgrounds and some have experience in leading HIV prevention programmes, including increasing PrEP access among underserved communities. **3. Unheard Voices** The Unheard Voices project is a collaboration between National AIDS Trust and One Voice Network, an independent collective of Black-led community organisations, seeking to improve the health and wellbeing of Black communities in the UK who are affected by HIV. The project aims to end structural inequalities by ensuring Black communities living with or at risk of HIV can hold decision-makers to account, influence actions, and become part of the decision-making process. The project has conducted research and advocacy on areas related to HIV prevention, and the experiences of Black-led communities and community-led organisations. **4. Discrimination Casework Service** National AIDS Trust provides advice and support to people living with or affected by HIV who have faced discrimination through our Casework Service.

[1] National AIDS Trust et al (2022) Not PrEPared. Available at: https://www.nat.org.uk/sites/default/files/publications/Not%20PrEPared.pdf

Living with the condition

6. How does being at risk of sexually acquiring HIV-1 affect people?	There remain structural and health barriers for people living with HIV from having a good health related quality of life. The recently published UKHSA and UCL 'Positive Voices 2022' report, highlights that people living with HIV experience poorer levels of wellbeing, care and quality of life compared to others.[2] People living with HIV are more likely to live in poverty, be unemployed and have higher levels of unmet needs in several key domains.[3] The emotional challenges subsequently result in worse outcomes for related quality of life & employment. Public polling shows HIV remains a highly stigmatised and misunderstood health condition.[4] For example, only a third of the UK public agreed they have sympathy for all people living with HIV and only a quarter knew about PrEP.[5] The Positive Voices report also highlights that 1 in 3 people had low self-esteem because of their HIV status, and 1 in 25 people had been verbally harassed because of their HIV status in the last year. Through NAT's Discrimination Casework service, we see how people living with or affected by HIV face discrimination in a range of settings including in the health service, employment and family settings. The impact of societal stigma and fear of judgement contributes to some people not taking oral PrEP in concern it could be mistaken for HIV treatment, particularly if someone is experiencing intimate partner violence. Communities disproportionately affected by HIV experience wider structural challenges which influence their health outcomes. People living with HIV are more likely to be living in poverty, with levels of poverty seen in people living with HIV aged 55+ double those seen in the general population. There are also worse prevention, treatment and care outcomes for particular communities, including women where HIV transmission rates have increased in England. There is a significant shortfall in the number of women being offered or accepting HIV tests; and a higher proportion of late HIV diagnoses amongst women. Women are placed at higher risk of sexually acquiring HIV because of factors that include intimate partner violence, worse access to mental health support compared to other groups, and challenges in accessing PrEP.

[2] UKHSA (2024) Positive Voices. Available at: https://www.gov.uk/government/pulications/hiv-positive-voices-survey/positive-voices-2022-survey-report
[3] ibid
[4] NAT (2021) HIV: Public Knowledge and attitudes. Available at: https://www.nat.org.uk/press-release/new-polling-shows-hiv-stigma-still-widespread
[5] ibid

7. What do people at risk of sexually acquired HIV-1 infection or carers (if applicable) think of current treatments and care available on the NHS?	Recent UKSHA data highlights that for those living with HIV, they report a high level of satisfaction with their HIV care service, with an average satisfaction rating of 9.4 out of 10.[6] These services would also be providing services (including HIV testing and prevention) for those at risk of acquiring HIV, but have been impacted by significant funding cuts. The public health grant has been cut by 26% on a real-terms per person basis since 2015/16 and one of the largest reductions in spend has been on sexual health services.[7] This has coincided with increased demand for sexual health services, with nearly 4.5 million consultations carried out in 2022, up by a third since 2013.[8] This has resulted in a reduction in councils' ability to spend on STI testing, contraception and treatment, and in turn, hampering efforts to offer holistic support to those at risk of acquiring hI . Reflecting the pressure that sexual health services are under, NAT and partners *'Not PrEPared'* report highlighted the challenges and delays which communities have faced in accessing PrEP.[9] Our research found that the most common waiting time for a PrEP appointment at a sexual health clinic in England was 12 weeks (35%).[10] Given that PrEP is still only available from level 3 sexual health clinics, alongside the introduction of injectable PrEP, greater access to PrEP through online provision, community pharmacies and GPs, could also alleviate some pressure and help clinics to do more to reach more people.

[6] UKHSA (2024) Positive Voices. Available at: https://www.gov.uk/government/publications/hiv-positive-voices-survey/positive-voices-2022-survey-report

[7] The Health Foundation (2023) Public health grant. Available at: https://www.health.org.uk/news-and-comment/charts-and-infographics/public-health-grant-what-it-is-and-why-greater-investment-is-needed#:~:text=The%20public%20health%20grant%20has,been%20allocated%20to%20local%20authorities.

[8] Local Government Association (2024) Breaking point: Securing the future of sexual health services. Available at: https://www.local.gov.uk/publications/breaking-point-securing-future-sexual-health-services

[9] National AIDS Trust et al (2022) Not PrePared. Available at: https://www.nat.org.uk/sites/default/files/publications/Not%20PrEPared.pdf

[10] ibid

8. Is there an unmet need for people at risk of sexually acquired HIV-1 infection?	Interventions are urgently needed to end widening disparities in HIV prevention and support communities that are at higher risk of acquiring HIV. Recent studies and UKHSA's own assessment has shown that we will not deliver the UK Government's HIV Action Plan target of ending new transmissions by 2030 without increasing access to PrEP. PrEP use, alongside other HIV combination prevention tools, has been a key factor in the significant reductions in HIV cases seen in England – particularly in gay and bisexual men who have sex with men (GBMSM). However, there are profound inequalities in the accessibility to PrEP which put women and BAME communities at higher risk of transmission. The English HIV and Sexual Health Commissioners Group's PrEP Insight Project Report found low PrEP awareness among Black African women, trans communities, and sex workers.[11] The recent UKHSA monitoring report for the HIV Action Plan found that GBMSM were consistently more likely than heterosexual men and women to have PrEP need, have that need identified and start or continue PrEP.[12] In 2022, PrEP need in GBMSM was 69%, of whom 84% had their PrEP need identified during a clinical consultation, and 74% initiated or continued PrEP. This compares to 1.8%, 63% and 38% in heterosexual men and 0.8%, 59% and 36% in heterosexual women, respectively.[13] Given these unmet needs, the Government has stated that in order to reach the interim HIV Action Plan 2025 targets it is a priority to 'improve access to PrEP for all groups in need, in particular heterosexual men and women, and ethnic minorities in all groups whilst supporting patient choice in relation to preference of prevention methods'. Providing access to CAB-LA would be a cost-effective intervention to address these unmet needs, support patient choice and deliver on ambitions of the HIV Action Plan.
9. Where would people prefer to go to receive prophylactic treatment? (hospital / GP surgery /pharmacy / other)	Interventions should be responsive to patient choice and reflective on how preference is likely to vary between different communities. For example, studies have shown that integrating a PrEP option into sexual and reproductive health services offers benefits for women who are less likely to access sexual health services compared to GBMSM.[14] Additionally, for trans communities, prophylactic treatment should be considered for gender identity services.

[11] English HIV and Sexual Health Commissioners Group (2023) PrEP Insights Project. Available: https://www.adph.org.uk/englishhivandsexualhealthcommissionersgroup/wp-content/uploads/sites/20/2023/08/EHSHCG-PrEP-Insight-Project-Full-Report.pdf

[12] UKHSA (2023) HIV Action Plan Monitoring and evaluation framework. Available at: https://www.gov.uk/government/publications/hiv-monitoring-and-evaluation-framework/hiv-action-plan-monitoring-and-evaluation-framework-2023-report#foreword

[13] ibid

[14] O'Malley et al (2021) Health Care Providers as Agents of Change: Integrating PrEP With Other Sexual and Reproductive Health Services for Adolescent Girls and Young Women. Available at:

Advantages of the technology

10. What do people at risk of sexually acquired HIV-1 infection or carers (if applicable) think are the advantages of the technology? ● How would having a prophylactic treatment available impact the lives of people at risk of sexually acquired HIV-1 (for example, how would it change the activities people do, or how they feel?) ● How would the effectiveness of treatment impact this?	CAB-LA is currently the most effective form of PrEP for people at high risk of contracting HIV, and is more discreet than the once-daily oral PrEP pill. CAB-LA has the potential to play a key role in addressing inequalities, increasing patient choice and supporting the delivery of the HIV Action Plan. The effectiveness of the technology, and studies from other countries, highlights CAB-LA's potential to be a key intervention in the UK's HIV prevention efforts, particularly amongst women. CAB-LA is the first and only PrEP modality that has proved highly effective in women. Global studies have highlighted that use of this World Health Organisation recommended medicine has resulted in a 79% relative reduction in HIV risk compared with oral PrEP, where adherence to taking daily oral medication often remains a challenge.[15] Long-acting injectable products have also been found to be acceptable and sometimes preferred in global studies examining community PrEP preferences.[16] A study from Imperial College found that injectable PrEP could prevent around 10% more new infections than tablets alone at similar levels of usage in the US.[17] The increased access of PrEP among GBMSM has been shown to positively contribute to key outcomes including their wellbeing, mental health with reduced anxiety, and having a healthy sex-life. With women and other communities having lower access to oral PrEP so not fully realising these benefits, a CAB-LA could help address these inequities. Access to a CAB-LA would also address challenges people face with pill burden which undermines adherence. Access to CAB-LA would also mitigate concerns that someone may have from taking oral PrEP if it is misinterpreted to be HIV treatment. This is because of concerns related to stigma, discrimination and intimate partner violence. Given that women at higher risk of acquiring HIV may experience intimate partner violence and not be in a position to negotiate safe sex, a CAB-LA would also give women more control and safety in their sex lives and relationships.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9580786/#:~:text=Integrating%20PrEP%20with%20other%20sexual%20and%20reproductive%20health%20(SRH)%20services, clients%20(14%E2%80%9317).

[15] WHO (20222) WHO recommends long-acting cabotegravir for HIV prevention. Available at: https://www.who.int/news/item/28-07-2022-who-recommends-long-acting-cabotegravir-for-hiv-prevention

[16] ibid

[17] Imperial College (2023) Long-acting PrEP injections could help reduce new cases of HIV in United States. Available at: https://www.imperial.ac.uk/news/242631/long-acting-prep-injections-could-help-reduce/

Disadvantages of the technology

11. What do people at risk of sexually acquired HIV-1 infection or carers (if applicable) think are the disadvantages of the technology?	Whilst CAB-LA holds strong promise in driving forward the UK's HIV prevention efforts, particularly amongst women and other groups with unmet needs, provision of the medicine shouldn't be made in isolation to other needed interventions. For example, the effective provision of oral and injectable PrEP access beyond sexual health services, which will help increase access to PrEP more widely amongst underrepresented, at-risk demographics. More funding should also be given to sexual health commissioners to fund more targeted outreach programmes. Given the current pressures in sexual health services, there could also be disadvantages in the delivery of the technology and concern that people may miss appointments. But this could be mitigated through allowing the provision of oral PrEP in other settings, including integrating a PrEP option into sexual and reproductive health services. Compared to oral antiretroviral medicines, a long-acting injectable is more complex to manufacture. Given this, plans should be put in place to ensure equitable supply across sites in the UK, and prevent any potential stock-outs.

12. Are there any groups of people at risk of sexually acquired HIV-1 infection who might benefit more or less from the technology than others? If so, please describe them and explain why.	Data suggests that not all people at risk of HIV-1 will need CAB-LA, further supporting how this would constitute a cost-effective intervention. The majority of oral PrEP users being GBMSM, take generic TD/FTC with high levels of acceptability. Recent UKHSA reporting notes that the proportion who initiated or continued PrEP rose slightly in GBMSM from 72% in 2021 to 74% in 2022.[18] It is expected that a small number of these people might require support with adherence or access to a long-acting injectable. The recent UK Government HIV Action Plan monitoring framework however highlights that PrEP uptake is lowest among heterosexual individuals with the highest need, among black African and Asian ethnicities.[19] We support THT's submission which notes that some people belonging to one or more of these HIV risk indicator groups might be more likely to find CAB-LA a better choice, or the only PrEP option suitable and effective for them: Female sex workers; Black African heterosexuals; The under 25s; People experiencing homelessness; People with substance misuse; People from minority ethnic groups; People experiencing domestic abuse/intimate partner violence; People accessing reproductive health and unplanned pregnancy services; Recent migrants

[18] UKHSA (2023) HIV testing, PrEP, new HIV diagnoses and care outcomes for people accessing HIV services: 2023 report. Available at: https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2023-report

[19] UKHSA (2023) HIV Action Plan Monitoring Frameworking. Available at: https://www.gov.uk/government/publications/hiv-monitoring-and-evaluation-framework/hiv-action-plan-monitoring-and-evaluation-framework-2023-report#concluding-remarks

Equality

13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Diagnoses have increased in the last year amongst heterosexual men and women, as well as GBMSM of other ethnicities. Communities beyond GBMSM are still not aware of PrEP, with no local authority reporting to us that more than 5 women are using their PrEP services.[20] Greater action must be taken to end the disparities in HIV prevention and specifically increase access to PrEP. Research suggests that CAB-LA could be a game-changer in ending these inequities at both a UK and global level. CAB-LA is both effective and has high acceptability in the key communities which the UK needs to focus on to achieve the HIV elimination targets. Women, particularly those born outside the UK, can face economic, cultural and language barriers to accessing sexual health services. For example, Black African women in the UK may prefer to access primary care for sexual health issues, rather than the sexual health clinics where PrEP is currently being provided. CAB-LA holds the potential for removing barriers to accessing PrEP for these communities, whilst advancing their sexual and reproductive health rights.

[20] National AIDS Trust et al (2022) Not PrEPared. Available at: https://www.nat.org.uk/sites/default/files/publications/Not%20PrEPared.pdf

Other issues

14. Are there any other issues that you would like the committee to consider?	As well as the public health advantages and being a key opportunity to reduce inequities in HIV prevention, there is an economic case. In 2016, the cost of HIV treatment per annum was estimated to be around £14,000 per case when HIV is diagnosed early, and £28,000 per case when diagnosed late.[21] Each HIV infection per person was estimated to represent between £280,000 and £360,000 in lifetime costs to the health system.[22] Given that CAB-LA may improve uptake, acceptability and adherence, particularly amongst communities that have lower access rates to oral medicines, the technology offers a strong return on investment through reducing HIV transmissions, and the human and economic costs associated with this.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	- Interventions and new technologies are urgently needed to end widening disparities in HIV prevention and deliver on the UK Government's HIV Action Plan. - CAB-LA has the potential to address inequities and barriers to PrEP access, particularly among women. - CAB-LA has the potential to positively improve the Quality of Life, address inequalities and create opportunities for communities that are at risk of HIV. - The economic case for CAB-LA is strong, with potential cost savings through reduced HIV transmissions and wider associated health, societal economic benefits. - Alongside provision of CAB-LA, additional interventions needed to ensure full potential of the technology. This includes expanding PrEP access beyond sexual health services and community outreach programmes.

Thank you for your time.

[21] NICE (2017) HIV testing. Available at: https://www.nice.org.uk/guidance/qs157/documents/briefing-paper
[22] ibid

Please log in to your NICE Docs account to upload your completed submission.

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The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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ViiV response to draft guidance consultation

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	ViiV Healthcare.

Please return to: **NICE DOCS**

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ViiV response to draft guidance consultation

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable.
Name of commentator person completing form:	ViiV Healthcare.

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ViiV response to draft guidance consultation

Summary of the comments

ViiV Healthcare (the company) would like to thank the committee for their consideration of cabotegravir for the prevention of human immunodeficiency virus-1 (HIV-1) acquisition. Cabotegravir is the first long-acting injectable pre-exposure prophylaxis (PrEP), and has demonstrated a statistically significant, superior benefit in reducing the risk of HIV acquisition compared with daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in both men who have sex with men and transgender women, and cisgender women at high risk of HIV acquisition. The company acknowledge the concerns of the committee and have sought to provide clarity on the issues raised throughout the draft guidance response document. In summary,

- The company accepts the committee's conclusion that whole population covered by the marketing authorisation should be considered in its decision making. The company's submission includes evidence of clinical effectiveness and cost-effectiveness of cabotegravir for the whole population in line with the marketing authorisation (i.e. individuals who take oral PrEP exactly as prescribed, those who do not as well as individuals who cannot take oral PrEP).

- There is clear unmet need for a new PrEP modality especially for those who do not or cannot take oral PrEP. In addition, new UKHSA data demonstrate widening health inequalities in new HIV acquisitions and PrEP usage (1), which the company hopes the committee will take into account in its decision-making.

- With PAS price, cabotegravir is a cost-saving use of NHS resources bringing increased QALYs and reduced lifetime costs compared with oral PrEP and no PrEP. These findings are consistent across scenarios and sensitivity analyses where cabotegravir continues to dominate oral PrEP and no PrEP, indicating that the parameter uncertainties potentially presented do not affect the conclusions of cost-effectiveness.

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ViiV response to draft guidance consultation

Table 1: Summary of the committee's preference and the Company's response

Parameter	Committee's preference	Company's response
Population	Whole population eligible for cabotegravir, including those who take oral PrEP exactly as prescribed.	Accept committee's conclusion – The original base-case reflects the whole population as per the licenced indication (the cost-effectiveness analyses presented represent individuals who take oral PrEP as prescribed and those who do not [cabotegravir vs. TDF/FTC] as well as those who cannot take oral PrEP due to contra-indication or difficulties with swallowing pills [cabotegravir vs. no PrEP]). However, it is anticipated that cabotegravir will be predominantly used by individuals with high unmet need for long-acting injectable PrEP (see comment 1). Additional scenario analysis provided explore the impact of varying TFV plasma levels on the model results.
Baseline risk of HIV acquisition	A baseline HIV acquisition value of 3.9 per 100 PY.	Accept committee's conclusion as a conservative assumption – base-case updated.
Duration of period of elevated risk of HIV acquisition	A HIV risk period of 10 years.	No change from original base-case - A HIV risk period of 5 years is assumed. Additional justification and explanation is provided exploring uncertainty around this parameter (see comment 3).
Transition from cabotegravir to TDF/FTC	Uncertain.	No change from original base-case – [redacted] transition is reasonable, particularly considering a population that reflects individuals who can take oral PrEP as prescribed in addition to those who cannot. Additional scenario analyses provided exploring uncertainty around this parameter (see comment 4).
Persistence improvement associated with cabotegravir	Uncertain.	No change from original base-case – 20% persistence improvement with cabotegravir is reasonable in light of clinical opinion and the evidence submitted. Additional scenario analysis provided exploring uncertainty (see comment 5).
Administration time	Cabotegravir administration costs to be based on 1 hour of clinic time.	No change from original base-case – Cabotegravir administration requires 30 min of nurse time for the first two injections and 20 min of nurse time for subsequent injections. Costs associated with visits and medical consultant time are costed separately in the model.

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ViiV response to draft guidance consultation

Parameter	Committee's preference	Company's response
		Additional justification and explanation provided (see comment 6).
Starting age of the modelled population	33 years.	Base-case updated following the publication of the 2024 UKHSA report using a similar approach as in the original base case. Additional justification and explanation provided (see comment 7).

Abbreviations: HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; PY, person years; RWE, real world evidence; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TFV: tenofovir; UK, United Kingdom.

Revised Company base case

The following changes have been made to the company's base case compared with the original cost-effectiveness analysis:

1. Baseline risk of HIV acquisition updated to 3.9 per 100 person-years (PY)
2. Discontinuation rate implementation corrected to apply rate for 6 months instead of 5 months
3. Error in the data selection from one study used in the indirect treatment comparison (ITC) corrected and uncertainty in adherence measurement incorporated
4. Starting age and population distribution updated in line with new data from the UKHSA (1).
5. Error in the frequency of renal function tests applied to cabotegravir and TDF/FTC in the cost-effectiveness analysis identified and corrected in line with the BHIVA/BASHH guidelines (2).

The impact of each individual change on the base-case results compared to TDF/FTC, as well as the revised company base-case results compared to TDF/FTC reflecting all changes is presented in Table 2 (cabotegravir vs. TDF/FTC) and Table 3 using the cabotegravir patient access scheme (PAS).

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ViiV response to draft guidance consultation

Table 2: Revised company deterministic base-case results cabotegravir vs. TDF/FTC (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
Previous company base-case results submitted at technical engagement							
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base-case results reflecting all changes made in response to draft guidance consultation							
TDF/FTC	[redacted]	[redacted]	**–**	**–**	**–**	**–**	**–**
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]
Baseline risk of HIV acquisition updated to 3.9 per 100 PY							
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Discontinuation rate implementation corrected							
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Error in the data selection from one study used in the indirect treatment comparison (ITC) corrected							
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Starting age and population distribution updated in line with new UKHSA data							
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Error in the frequency of renal function tests applied to TDF/FTC and cabotegravir							
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; Incr., incremental; ITC, indirect treatment comparison; PAS, patient access scheme; PY, person-years; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UKHSA, United Kingdom Health Security Agency.

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

ViiV response to draft guidance consultation

Table 3: Revised company deterministic base-case results cabotegravir vs. no PrEP (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
Previous company base-case results reflecting all changes (technical engagement)							
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base-case results reflecting changes made in response to draft guidance consultation							
No PrEP	[redacted]	[redacted]	**–**	**–**	**–**	**–**	**–**
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	[redacted]	[redacted]
Baseline risk of HIV acquisition updated to 3.9 per 100 PY							
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Discontinuation rate implementation corrected							
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Error in the data selection from one study used in the indirect treatment comparison (ITC) corrected							
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Starting age and population distribution updated in line with new UKHSA data							
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Error in the frequency of renal and bone function tests applied to cabotegravir and TDF/FTC							
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; Incr., incremental; ITC, indirect treatment comparison; PAS, patient access scheme; PY, person-years; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UKHSA, United Kingdom Health Security Agency.

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

ViiV response to draft guidance consultation

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Background Despite current combination prevention efforts contributing to a decline in HIV transmissions, there is a substantial unmet need for additional preventative medicines in England. The United Kingdom (UK) is still projected to miss the UK HIV Action Plan's target of zero new transmissions by 2030 (3). The latest data from the UK Health Security Agency (UKHSA), released on the 1st October 2024 (subsequent to the Company's submission), has shown that although the number of people taking PrEP has increased annually since it was commissioned by the National Health Service (NHS) in 2020, the initiation or continuation of PrEP among those with a PrEP need still remains low in certain populations, including heterosexual men (39.0%), and heterosexual and bisexual women (40.9%) (1). The UKHSA's report states that "inequalities in access remain ongoing, with unmet needs by specific exposure groups" (1). • The number of new HIV diagnoses first made in England has increased by 15% from 2,451 in 2022 to 2,810 in 2023 (1). • The steepest rise in new HIV diagnoses first made in England was among people exposed through sex between men and women, with an increase of 32% between 2022 and 2023, accounting for almost half (49%) of new diagnoses made in England in 2023 (1). • The greatest increase among those exposed by heterosexual contact was among people of Black African ethnicity (64%) (1). • Men exposed by sex between men accounted for almost a third (29%) of new diagnoses first made in England in 2023 (1). • Despite the recent trend towards a decline in the number of new among men that have sex with men, new HIV diagnoses first made in England also increased in this group by 7% between 2022 and 2023 (1). • Similar to those exposed by heterosexual contact, the greatest increase in new diagnosis among men that have sex with men was observed among men of Black African ethnicity (1). The UKHSA's report acknowledges the "disproportionate rise" among ethnic minority groups as "further evidence of widening inequalities" (1). Taken together, these data indicate that sustained, and additional efforts are still required to end HIV transmissions in England. Cabotegravir, the first and only licensed long-acting injectable PrEP, offers a much-needed new modality with reduced administration frequency. It potentially addresses some of the limitations associated with the current oral PrEP options, for example providing a more discreet protective option without any need to hide pill bottles, potentially alleviating concerns around PrEP-related stigma and confidentiality, and an alternative modality/dosing regimen may better suit some individuals needs/preferences or alleviate their adherence challenges. Additionally, Cabotegravir offers superior efficacy compared to the existing standard of care (4, 5), which will support individuals HIV prevention needs and the UK government's action plan to reach zero HIV transmissions by 2030 (6). Cabotegravir also supports shared decision-making through offering more dynamic choice of HIV prevention modalities, which has been shown to increase biomedical covered time and reduce HIV incidence (7). Shared decision-making is a core component of the NHS Constitution (8, 9), with the National Institute for Health and Care Excellence (NICE) providing recommendations to help increase its use in day-to-day clinical practice (NG197) (10).

	The company kindly request that the committee consider the aforementioned factors, and the clarifications and new economic model results presented in this response when assessing cabotegravir for the prevention of HIV-1 in adults and young people.
1	**Positioning of cabotegravir** In the draft guidance, the committee acknowledged the difficulties in defining the population of people who do not take oral PrEP exactly as prescribed and concluded that it could only make recommendations within the full marketing authorisation for cabotegravir. While the decision problem population in the company's original submission was chosen in order to position cabotegravir for use in people with the highest unmet PrEP needs, and therefore, where it is most likely to be used in clinical practice, the company agrees with the committee that identifying individuals who are sub-optimally adherent to oral PrEP may be difficult in the real world and therefore some individuals may receive cabotegravir despite oral PrEP being an appropriate option for them (i.e. they are optimally adherent to oral PrEP). The company would like to clarify that these individuals have already been captured in the original submission within the underpinning clinical and cost-effectiveness evidence, which was based on the population for the full marketing authorisation. **The clinical evidence presented represents a population of individuals who take oral PrEP as prescribed and those who do not.** The inclusion criteria of HPTN 083 and HPTN 084 are aligned with cabotegravir's marketing authorisation, and the population within each trial is a mix of individuals with optimal and suboptimal adherence; this is acknowledged within the draft guidance, where the committee comment that "*the clinical trial populations would have included people who took oral PrEP exactly as prescribed, as well as those who did not*". The trials are also considered to be generalisable to UK individuals at high risk of HIV acquisition, as recognised by clinical experts at a UK advisory board (11) and by a clinical expert consulted during the appraisal process, as stated in the draft guidance. **The cost-effectiveness analysis of cabotegravir vs. TDF/FTC represents a population of individuals who take oral PrEP as prescribed and those who do not. The totality of the HPTN 083 and HPTN 084 data was used in the health economic model for this comparison in the original submission and assumed to lead to a conservative estimate of cost-effectiveness for the subpopulation of people with the greatest unmet need.** To estimate the effectiveness of TDF/FTC relative to no PrEP, the cost-effectiveness model uses the ITC, which includes a meta-regression component estimating the effectiveness of TDF/FTC based on the proportion of the population with detectable tenofovir (TFV) plasma levels (as measured by plasma TFV concentrations ≥ 0.31 ng/mL). Plasma TFV concentrations refer to the levels of the drug tenofovir present in blood plasma. In the economic model, the effectiveness estimated from the indirect treatment comparison (ITC) for cabotegravir vs. no PrEP and TDF/FTC vs. no PrEP is applied to the baseline risk of HIV acquisition to derive the HIV incidence associated with TDF/FTC and cabotegravir. In the base case cost-effectiveness analysis, the company used the HPTN 083 and HPTN 084 trial populations to determine the proportion of individuals with detectable TFV plasma levels: • In the HPTN 083 trial, the proportion of people with detectable TFV plasma levels was 86% (which when input into the meta-regression equation from the ITC gives an estimate of effectiveness of TDF/FTC vs. no PrEP of [redacted]). • In HPTN 084, the proportion of people with detectable TFV plasma levels was 56% (which when input into the meta-regression equation from the ITC gives an estimate of effectiveness of TDF/FTC vs. no PrEP of [redacted]).

The proportion of people with TFV plasma levels corresponding to high adherence to TDF/FTC ([redacted] TFV plasma levels corresponding to ≥4 TDF/FTC pills per week in HPTN 083 and 42% TFV plasma levels corresponding to daily use of oral PrEP in HPTN 084) was used to inform the costs of TDF/FTC in the model.

At the time of the original submission, the company recognised that the proportion of individuals with detectable TFV plasma levels (and the proportion of individuals with TFV levels corresponding to high adherence to oral PrEP in HPTN 083) in the economic model represented a conservative estimate of the cost-effectiveness of cabotegravir vs. TDF/FTC for a population of individuals with suboptimal adherence to oral PrEP. This is because the base-case analysis reflected the populations in the HPTN 083 and HPTN 084 trials which represents an "all comers" population, including individuals who take oral PrEP as prescribed as well as those who do not, as recognised by the committee in the draft guidance. Consequently, the company considers that the base case previously considered is appropriate to inform the cost-effectiveness analysis of cabotegravir vs. TDF/FTC in a population of individuals who can take oral PrEP (as prescribed or not).

Scenario analysis: the proportion of the population with detectable tenofovir (TFV) plasma levels is set to 100%.

A new scenario analysis has been provided, reflecting the effectiveness of TDF/FTC that could be observed in a hypothetical population where 100% of individuals have detectable TFV plasma levels for both men who have sex with men and transgender women, and cisgender women populations. This scenario analysis explores the impact on the economic model results of setting the proportion of individuals with detectable TFV plasma levels to the highest value. However, even with this extreme scenario, cabotegravir at PAS price remains dominant vs. TDF/FTC, demonstrating that the economic analysis results are robust to changes in the proportion of individuals with detectable TFV plasma levels.

In light of the HPTN trials results and evidence available in the literature, a population in which 100% of individuals have detectable TFV plasma level is unlikely to be clinically plausible. Consequently, this scenario should be considered to test the robustness of the economic model results but should not be used as the base case.

The results of this scenario are presented in Table 4 and indicate that the conclusions from the base case analysis (i.e. cabotegravir dominates TDF/FTC) are robust to changes in the detectable TFV plasma level parameter in the model.

Table 4: Scenario analysis results for cabotegravir versus TDF/FTC in the population where 100% of individuals have detectable TFV plasma levels (applied to both men who have sex with men/transgender women and cisgender women) (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; PAS, patient access scheme; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TFV, tenofovir.

Feasibility of a cost-effectiveness analysis in a population of individuals taking oral PrEP as prescribed

The company would like to note that modelling the cost-effectiveness of a population of individuals who take oral PrEP exactly as prescribed would not be clinically plausible. Indeed, for the same reasons that it is not feasible to identify individuals who do not take oral PrEP as prescribed (as noted by the committee "*The committee also noted that people who do not take oral PrEP exactly as prescribed cannot be identified using defined characteristics"*) identifying this population in real-

	life would not be feasible. Instead, the company considers that the approach selected in the base case analysis, reflecting the HPTN trial population (an "all comers" population) is the most appropriate approach to evaluate the cost-effectiveness of cabotegravir vs. TDF/FTC in the population considered in this appraisal.
2	**People who cannot take oral PrEP** The draft guidance states that "*The evidence does not cover everyone who could have cabotegravir in NHS clinical practice. Because of this, it is not possible to determine the cost-effectiveness estimate for the whole population without further analyses from the company*". In response, the company would like to note that in the original submission, comparisons were conducted for TDF/FTC in the 'all-comers' population of individuals taking oral PrEP (both optimally and sub-optimally), as well as no PrEP for individuals who cannot take oral PrEP. Specifically, the committee noted that everyone in the clinical trials had oral TDF/FTC or an oral placebo. It concluded that the clinical trial populations did not include people who cannot take oral PrEP because of medical contraindications or difficulties swallowing tablets. The committee noted that these factors introduced considerable uncertainty about whether the results from the company's economic model were applicable to the company's defined decision problem population. The committee also noted that some people who cannot take oral PrEP will have contraindications to oral PrEP but not cabotegravir, and therefore concluded that no PrEP should be considered a comparator for those who cannot take oral PrEP because of contraindications or limitations swallowing pills. The committee did however comment that there is uncertainty around whether it was possible to make this comparison from the evidence submitted for the evaluation. The company agrees with the committee that some people who cannot take oral PrEP due to contraindications will be eligible for cabotegravir, and with the committee's view that the most appropriate comparison is for cabotegravir vs. no PrEP. The company would like to highlight that: • Individuals who are not eligible for oral PrEP or cannot take oral PrEP are not represented in the HPTN trials, as for ethical reasons it was not appropriate to include a placebo arm (12) • The clinical systematic literature review (SLR) identified studies with placebo arms or no PrEP groups which were included in the indirect treatment comparison (ITC) of cabotegravir vs. no PrEP and TDF/FTC vs. no PrEP (see Appendix D of the Company evidence submission) • The effectiveness of cabotegravir vs. no PrEP estimated via the ITC is generalisable to the population of individuals who are contraindicated to oral PrEP or have difficulties swallowing pills. Neither contraindication to oral PrEP nor difficulties swallowing pills are expected to be treatment effect modifiers in the relative efficacy estimates of cabotegravir vs. no PrEP. Therefore, the results of the ITC and the conclusion of the cost-effectiveness analysis vs. no PrEP (i.e. cabotegravir dominated no PrEP) are applicable to the population who cannot take oral PrEP.
3	**Duration of HIV risk period** In the draft guidance, the committee noted that there was uncertainty associated with using a single at-risk period for HIV acquisition in the model, so it was appropriate to use a conservative estimate for this assumption. However, the draft guidance notes that clinical expert opinion heard at the first appraisal consultation meeting explained that "there are multiple components that define HIV risk and most of them do not stay constant over time, so [the expert] considered that 5 years is a more appropriate estimate for the at-risk period of HIV acquisition". The company notes that the decision to select the 5-year duration of risk was informed by real-world evidence of persistence to TDF/FTC. These data demonstrate a high rate of discontinuation of TDF/FTC (over 40% of people at 12 months) (13) and extrapolation of the real-world

persistence data in the economic model leads to a decreasing proportion of individuals on PrEP and an increasing proportion of individuals on no PrEP over time so that in both the TDF/FTC and cabotegravir arms, the proportion of individuals who remain on PrEP after 5 years is 15% or lower. Considering extended periods of elevated risk where the majority of individuals have discontinued their PrEP modalities is not appropriate for comparing the cost-effectiveness of PrEP modalities.

The aforementioned clinical opinion, and the real-world evidence on persistence supports a 5-year duration of risk.

For completeness, the results of a scenario analysis exploring a 10-year is presented in Table 5 (cabotegravir vs. TDF/FTC) and Table 6 (cabotegravir vs. no PrEP). Cabotegravir remains dominant versus both TDF/FTC and no PrEP in this scenario but the company notes that this conservative scenario is associated with uncertainty and is not supported by evidence.

Table 5: Scenario analysis results for cabotegravir versus TDF/FTC 10-year period of elevated risk (cabotegravir PAS price)

Technologies	**Total costs (£)**	**Total QALYs**	**Incr. costs (£)**	**Incr. QALYs**	**ICER versus baseline (£/QALY)**
TDF/FTC	[redacted]	[redacted]			
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; PAS, patient access scheme; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TFV, tenofovir.

Table 6: Scenario analysis results for cabotegravir versus no PrEP 10-year period of elevated risk (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
No PrEP	[redacted]	[redacted]			
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; PAS, patient access scheme; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TFV, tenofovir.

4	**Transitioning from cabotegravir to TDF/FTC** In the draft guidance, the committee noted "*the proportion transitioning to TDF/FTC appeared high given the population, so it would be useful to know how the company calculated the exact proportion of people that transitioned from cabotegravir to TDF/FTC*." Section 4.4 of the summary of product characteristics (SmPC) for cabotegravir outlines the use of an alternative not long-acting form of PrEP to be taken in the months after discontinuation of cabotegravir (14). The Company notes that since the full population (people who take oral PrEP as prescribed and those who do not) is being considered in the base-case cost-effectiveness analysis, it is reasonable to assume that about [redacted] of people will take TDF/FTC after discontinuation of cabotegravir. Unfortunately, no additional data are available to support the assumption, however to acknowledge that the population contains people with lower and higher adherence to TDF/FTC, the company have conducted scenario analyses assuming [redacted] and [redacted] of people transition from cabotegravir to TDF/FTC. The company would like to note that in the cost-effectiveness analysis of cabotegravir vs. no PrEP (representing people who cannot take oral PrEP) the updated company base case submitted in response to technical engagement assumed that no individuals transition to TDF/FTC after discontinuation of cabotegravir. The results of the scenario analyses are presented in Table 7. In both scenarios, cabotegravir remains dominant vs. TDF/FTC. **Table 7: Scenario analysis results for cabotegravir versus TDF/FTC with [redacted] and [redacted] of people transitioning from cabotegravir to TDF/FTC (cabotegravir PAS price)**

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
[redacted] of people transition from cabotegravir to TDF/FTC					
TDF/FTC	[redacted]	[redacted]			
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
[redacted] of people transition from cabotegravir to TDF/FTC					
TDF/FTC	[redacted]	[redacted]			
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; PAS, patient access scheme; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Discontinuation in HPTN trials

The committee was unsure why the company had not used data from the HPTN trials to inform discontinuation probabilities and persistence for cabotegravir and oral PrEP, and it would have preferred to see these data used.

The company notes that discontinuation from HPTN 083 and HPTN 084 was reported as adverse events (AE) leading to discontinuation as a function of safety reporting, including HIV acquisition, use of prohibited concomitant medication, low adherence according to protocol, clinical or laboratory AE, clinical management committee (CMC) recommendation based on clinical, laboratory or psychosocial reasons, and participant request (unwilling or unable to comply with required study procedures). Consequently, the trials discontinuation data was reflective of clinical trial procedures, not a proxy for continuation or a person's willingness to continue taking a prescribed intervention for a given length of time. In addition, the trials are double blinded, therefore it is not possible to attribute discontinuation to either modality (oral or injection). As such, reporting discontinuation from trial data as a proxy for persistence would be unlikely to be representative of real-world usage. Persistence has not been reported by HPTN 083 or HPTN 084.

Persistence implementation in the cost-effectiveness model

The draft guidance states that the committee was unsure why a 20% improved persistence with cabotegravir was applied for the entire at-risk period of HIV acquisition, when the Company's calculated discontinuation probabilities for cabotegravir and TDF/FTC were equal at 12 months.

The company would like to highlight that a 20% improvement in persistence with cabotegravir is not applied for the entire at-risk period in the economic model. Rather, a 20% improvement in persistence is applied only in the first 6 months. As higher persistence leads to more people remaining on PrEP in the first 6 months, the larger pool of people on cabotegravir carries through to the remainder of the at-risk period; however, the discontinuation probabilities applied after the first 6 months are equal for cabotegravir and TDF/FTC. The discontinuation probabilities applied in the model are presented in Table 8.

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Table 8: Calculated probabilities of discontinuation for cabotegravir and TDF/FTC

	Cabotegravir injections	Oral PrEP (TDF/FTC)
Monthly discontinuation probability over the first 6 months	2.82%	5.73%
Monthly discontinuation probability after 6 months	3.30%	3.30%

Abbreviations: PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Persistence improvement with cabotegravir in a broad population of individuals who take oral PrEP as prescribed as well as those who do not

The draft guidance also notes that if the company's analyses were to include the whole population eligible for cabotegravir, including those who currently take TDF/FTC exactly as prescribed, there would be a much smaller improvement in persistence with cabotegravir.

The company stresses that persistence and adherence are distinct outcomes. Regardless of the level of adherence to oral PrEP, the ability for people to choose the modality that works best for them will improve their persistence with that modality; evidence from contraceptives has shown that matching people's preferred modality increased persistence (15).

Persistence refers to a person's willingness to continue taking a prescribed treatment for a given length of time (16). Inclusion of the whole population eligible for cabotegravir in the analysis enables inclusion of both people who do not or cannot take oral PrEP, and people who are optimally adherent to oral PrEP and choose cabotegravir. This means that cabotegravir for PrEP would address unmet need and preference. When a structured choice between oral PrEP and cabotegravir is provided through shared decision making, outcomes are improved including increased biomedical covered time and reduced HIV incidence (7). Shared decision making is a

key component of universal personalised care when people make choices about their treatment, care, and prevention of illness (9, 10). Generally, shared decision making improves persistence (17). Providing cabotegravir for PrEP to address unmet needs and preference, will not result in lower persistence in a broader population, because the intervention will be meeting people's needs and preferences.

Additional evidence supporting cabotegravir persistence

In the economic analysis, 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% for the first 6 months (95% CI 80.9−88.9%) (18).

Scenario analysis: the persistence improvement with cabotegravir is 10% compared to TD/FTC

The company notes the committee's concerns about the uncertainty around the percentage improvement in persistence with cabotegravir and have conducted scenario analyses assuming only a 10% improvement. The results of the scenario analysis are presented in Table 9 (cabotegravir vs. TDF/FTC) and Table 10 (cabotegravir vs. no PrEP) using the cabotegravir PAS price.

Consistently with the base case results, when considering a conservative estimate of persistence cabotegravir continues to dominate vs. TDF/FTC and no PrEP.

Table 9: Scenario analysis results for cabotegravir versus TDF/FTC, 10% improvement in persistence with cabotegravir (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]			
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; PAS, patient access scheme; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 10: Scenario analysis results for cabotegravir versus no PrEP, 10% improvement in persistence with cabotegravir (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]			
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; PAS, patient access scheme; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

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Cabotegravir administration costs

The draft guidance states that the committee concluded that cabotegravir administration costs should be based on 1 hour of clinic time for all visits.

The Evidence Assessment Group (EAG) commented that it was not appropriate for the company to assume that appointments for subsequent injections would only take 20 minutes, because evidence showed that appointments for cabotegravir and rilpivirine injections took longer than this (30 to 60 minutes). A clinical expert explained that extra time would need to be factored into each appointment for monitoring after the injection, HIV tests, and a sexual health screen.

The company notes that the cabotegravir administration time of 20 minutes for subsequent injections in the submitted model represents only the Band 5 nurse's time spent administering the injection. However, the model base case also incorporates 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

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administration time. The model assumes that the full cost of the 30-minute visit with a medical consultant will be charged 100% of the time to account for time spent on counselling, HIV testing and sexual health screen during injection visits.

The EAG's preferred assumption implies that each subsequent injection visit will take 90 minutes as it applies 20 minutes of Band 5 nurse time for observation, 40 minutes of clinical activity and 30 minutes of medical consultant time. This assumption represents double counting as the 30 minutes of medical consultant time already incorporates clinical activity and/or observation, as required. The company stresses that 90 minutes for a subsequent visit is highly unrealistic, as a UK multicentre service evaluation of injectable HIV treatment (cabotegravir and rilpivirine) pathways showed that appointments took between 30 to 60 minutes, and were 40 minutes or less in 78% of NHS HIV clinics (19), and cabotegravir for PrEP requires one injection without cold-chain storage compared to two injections with a cold-chain storage requirement for injectable HIV treatment.

A summary of the administration and visit costs included in the model base case is presented in Table 11.
Table 11: Administration and visit costs for cabotegravir
<table>
<tr><th></th><th>Band 5 nurse time (costed at £47.39 per hour)</th><th>Medical consultant time (costed at £116.41 per hour)</th><th>Total time per visit</th><th>Total cost per visit</th></tr>
<tr><td>First two injections</td><td>30 minutes</td><td>30 minutes</td><td>60 minutes</td><td>£81.90</td></tr>
<tr><td>Subsequent injections</td><td>20 minutes</td><td>30 minutes</td><td>50 minutes</td><td>£74.00</td></tr>
</table>
In conclusion, the company believes that the costs used in the base case in the original submission are appropriate.
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Starting age of people in the model

In the draft guidance, the committee concluded that the starting age of 33 selected by the EAG was more appropriate to use in the cost-effectiveness model (CEM). This figure is approximately the median age of people using PrEP in the UK, according to a cross-sectional study (20).

New UKHSA data up to 2023 show that the median age of individuals accessing oral PrEP, including men who have sex with men, transgender women, and cisgender women, falls within the 25–34 age range (21). Based on the assumption of a uniform age distribution within the population, the Company estimates the median age to be 34.0 years for men who have sex with men and transgender women, and 31.5 years for cisgender women.

The Company maintains that the age at the midpoint of the 5-year period of elevated risk should correspond to the cohort's median age, suggesting that the starting age for these cohorts in the model should be 2.5 years younger than the estimated median from UKHSA data. Therefore, the revised base-case analysis uses a starting age of 31.5 years for men who have sex with men and transgender women and 29.0 years for cisgender women.

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 from UKHSA data so that the modelled cohorts reflect the age of UK individuals at high risk of HIV acquisition.
</td></tr>
</table>

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

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8	**Underlying risk of HIV acquisition** The company accepts 3.9 per 100 person years (PY) as a conservative estimate of the underlying HIV risk.
9	**New version of UKHSA data** Since the initial submission, the 2024 UKHSA report on HIV testing, PrEP, new HIV diagnoses and care outcomes for people accessing HIV services has been released (1). This latest data release (reporting 2023 data) shows that there has been an increase in HIV acquisitions first diagnosed in England across every population (men exposed through sex with men, and people exposed by sex between men and women) between 2022 and 2023. The previous data release (reporting 2022 data) was used to inform the population distribution and starting age in the initial cost-effectiveness analysis. The 2024 publication reported that 94,026 of the 97,116 people eligible for PrEP (96.82%) were men who have sex with men and transgender women, while 3,090 (3.18%) were cisgender women. Based on the latest data release, the calculated median age was 34.0 years for men who have sex with men and transgender women, and 31.5 years for cisgender women. As described in comment 7, the starting age of the model was adjusted so that the median age aligns with the of the duration of the period of elevated risk. A summary of the model changes resulting from the UKSHA 2024 report is provided in Table 12.

Table 12. Changes to the model parameters updates reflecting 2024 UKHSA report

Model parameter	Previous base case (UKSHA 2023)	Updated base case (UKHSA 2024)
% men who have sex with men and transgender women	96.86%	96.82%
% cisgender women	3.14%	3.18%
Starting age (men who have sex with men and transgender women)	31 years	31.5 years
Starting age (cisgender women)	29 years	29 years

The cost-effectiveness results after updating the population distribution and starting age are presented using the cabotegravir PAS price in Table 13 vs TDF/FTC, and in Table 14 vs no PrEP. Changes resulting from the UKHSA report update had a minimal impact on cost-effectiveness results.

Table 13: Base-case cost-effectiveness results for cabotegravir versus TDF/FTC, updated UKHSA data (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; UKHSA, United Kingdom Health Security Agency.

Table 14: Base-case cost-effectiveness results for cabotegravir versus no PrEP, updated UKHSA data (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
No PrEP	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; UKHSA, United Kingdom Health Security Agency.

10

Updated indirect treatment comparison

An error in the extraction of data informing the ITC has been identified. This error was related to the extraction of data from the Partners PrEP study (22), where data were extracted on the efficacy of TDF arm rather than the TDF/FTC arm. The relative risk (RR) of HIV acquisition from the TDF arm in the study was originally included in the ITC as 0.37 for the male heterosexual population and 0.29 for the female heterosexual population (i.e. 63% and 71% efficacy, respectively). However Baeten et al, 2012 (22) reports “As compared with placebo, among women, the efficacy of TDF was 71% (P=0.002) and of TDF–FTC 66% (P=0.005); among men, the efficacies were 63% (P=0.01) and 84% (P<0.001), respectively”.

Further refinement of the ITC was undertaken to address concerns raised by the EAG 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 (key issue 5). The analysis was re-run using the correct data for TDF/FTC and allowing for measurement error in the reported adherence levels to be accounted for. The company notes that the EAGs’ approach was extended to take into account that, in a number of studies plasma samples were taken to estimate adherence in all patients who acquired HIV (seroconverted) and a sample of patients who did not acquire HIV. For these studies, binomial distributions were used to estimate adherence in those who did and did not acquire HIV and a separate binomial distribution to estimate the proportion of patients who did seroconvert. These were then combined to obtain a weighted average estimate for adherence. As found previously by the EAG, the incorporation of measurement error in adherence levels represents an improvement in the methodological approach but has very minimal impact on the results.

A summary of the changes to the model parameters resulting from the updated ITC base-case log relationship model for the comparison of TDF/FTC vs. no PrEP and cabotegravir vs. no PrEP in both the HPTN 083 and 084 population is presented in Table 15 below.

Table 15. Changes to the model parameters updates reflecting corrected errors in the ITC

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

Cabotegravir at PAS price remains dominant vs both TDF/FTC and no PrEP in the cost-effectiveness analysis using the updated ITC results as presented in Table 16 (vs TDF/FTC), and in Table 17 (vs no PrEP).

Table 16: Base-case cost-effectiveness results for cabotegravir versus TDF/FTC, updated ITC data (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; ITC, indirect treatment comparison; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 17: Base-case cost-effectiveness results for cabotegravir versus no PrEP, updated ITC data (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
No PrEP	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; ITC, indirect treatment comparison; NHB, net health benefit; PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

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11

Discontinuation rate implementation error identified and corrected.

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

The cost-effectiveness results after correcting the discontinuation implementation error are consistent with the base case results, as presented in Table 18 (vs TDF/FTC), and in Table 19 (vs. no PrEP).

Table 18: Base-case cost-effectiveness results for cabotegravir versus TDF/FTC, updated discontinuation rate implementation (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 19: Base-case cost-effectiveness results for cabotegravir versus no PrEP, updated discontinuation rate implementation (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
No PrEP	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

12

Frequency of renal function tests for cabotegravir and TDF/FTC implementation error identified and corrected.

An error in the implementation of health care resource use associated with renal function tests for TDF/FTC and cabotegravir has been 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 is crucial due to potential risks associated with the use of tenofovir disoproxil. These risks include renal failure, renal impairment, elevated creatinine levels, hypophosphatemia, and proximal tubulopathy, which may include Fanconi syndrome. In line with the BHIVA/BASHH guidelines (2), tests of kidney function (eGFR, urinalysis, serum creatinine) should be assumed to occur at baseline and at least once a year for those on TDF/FTC.

The SmPC for cabotegravir does not recommend testing of kidney function, as there is no link between cabotegravir and renal impairment, therefore these monitoring costs were removed for the cabotegravir arm in the model (14).

Base-case results after updating the HCRU for renal function monitoring are presented using the cabotegravir PAS price in Table 20 vs TDF/FTC, and in Table 21 vs no PrEP. Updating the model to more accurately reflect testing requirements led to similar conclusions as the base case analysis, cabotegravir is dominant vs. TDF/FTC and no PrEP.

Table 20: Base-case cost-effectiveness results for cabotegravir versus TDF/FTC, updated HCRU for testing of kidney function (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 21: Base-case cost-effectiveness results for cabotegravir versus no PrEP, updated HCRU for testing of kidney function (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
No PrEP	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Appendix A: Sensitivity analysis for revised base case

Probabilistic sensitivity analysis

Table 22: PSA base-case cost-effectiveness results for cabotegravir versus TDF/FTC (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

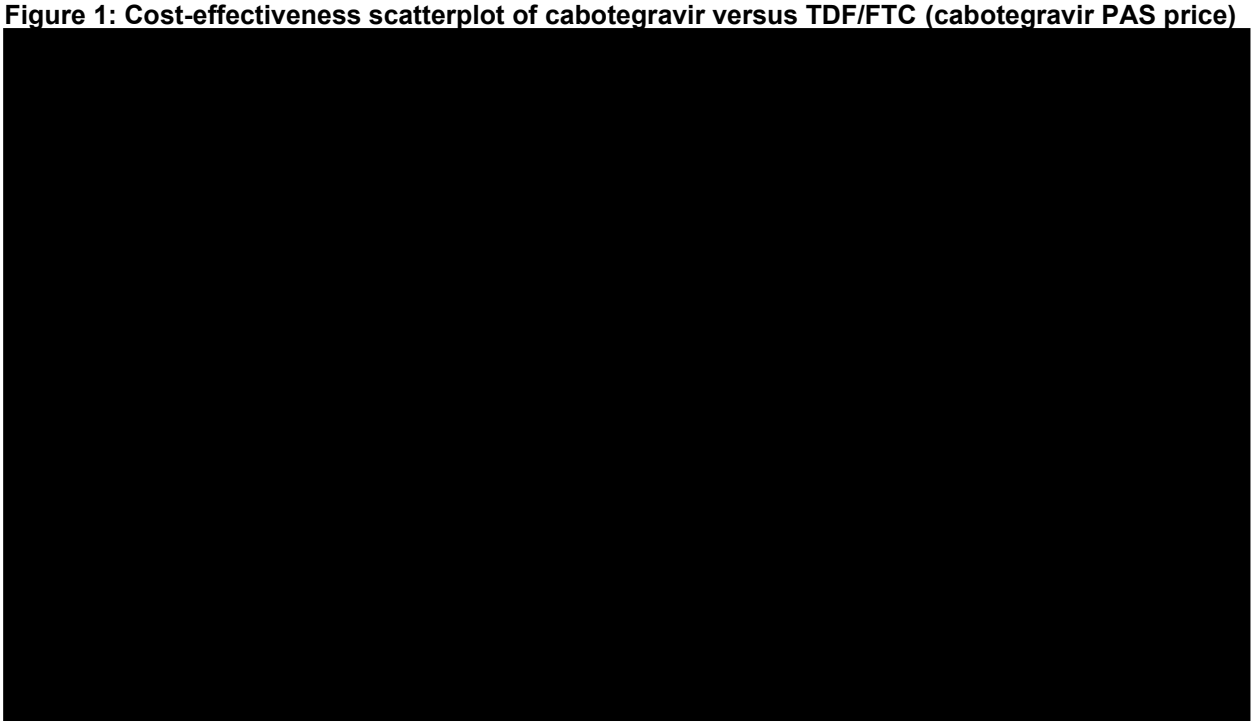
Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 23: PSA base-case cost-effectiveness results for cabotegravir versus no PrEP (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

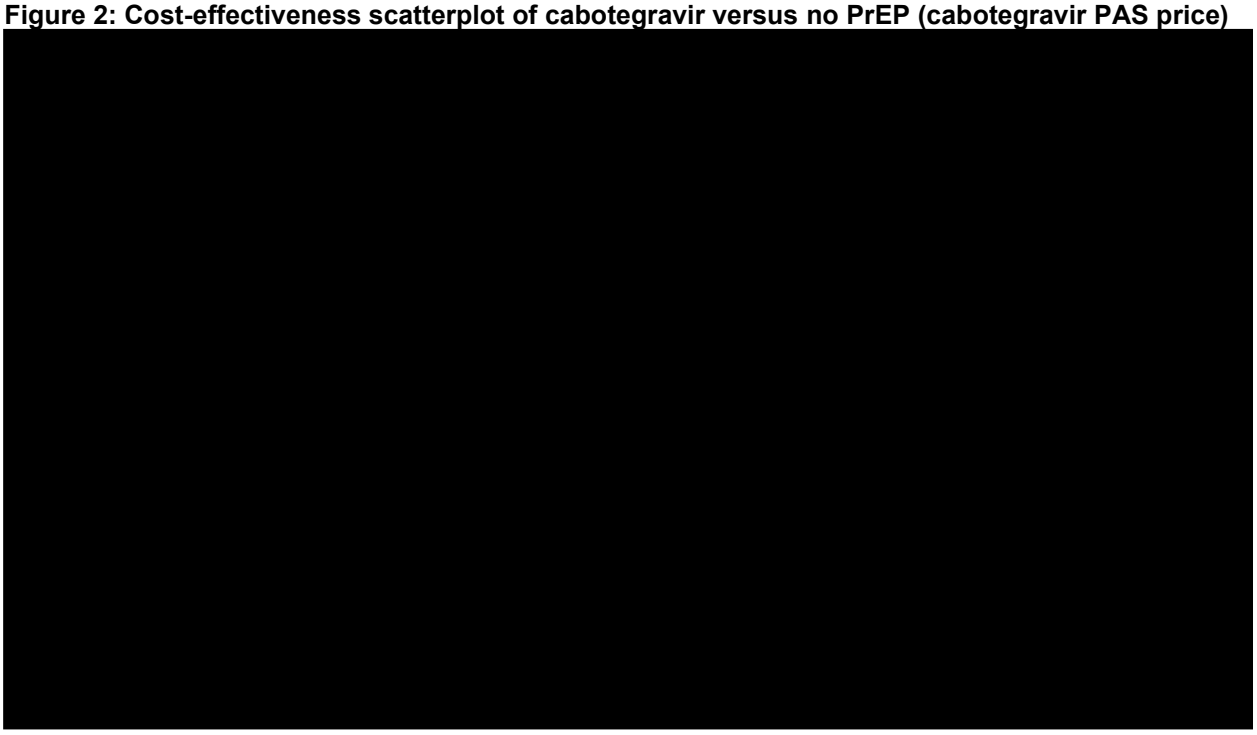
Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 1: Cost-effectiveness scatterplot of cabotegravir versus TDF/FTC (cabotegravir PAS price)



Abbreviations: PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 2: Cost-effectiveness scatterplot of cabotegravir versus no PrEP (cabotegravir PAS price)



Abbreviations: PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

Figure 3:Cost-effectiveness acceptability curve of cabotegravir versus TDF/FTC (cabotegravir PAS price)

Abbreviations: PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 4:Cost-effectiveness acceptability curve of cabotegravir versus no PrEP (cabotegravir PAS price)

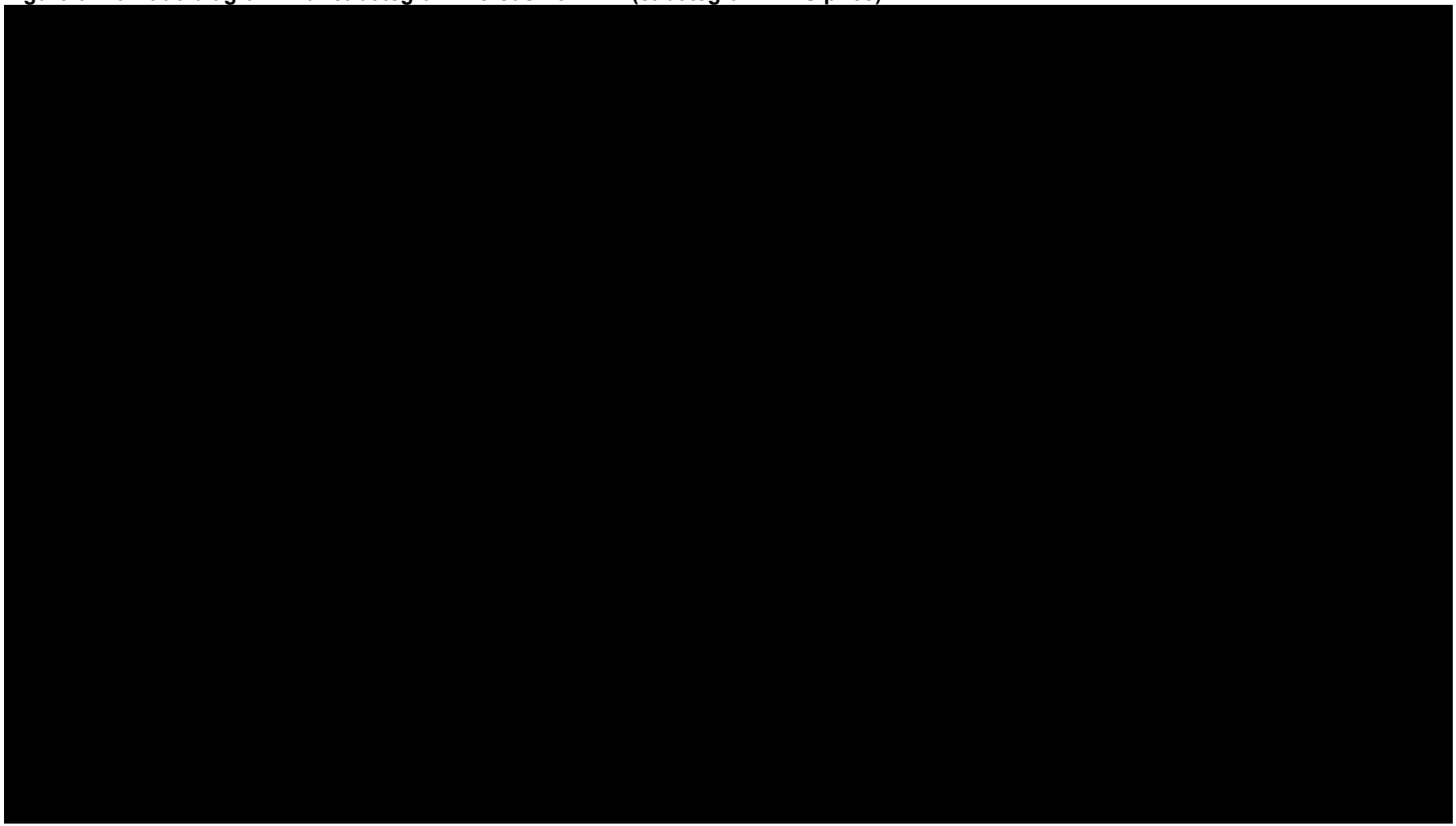
Abbreviations: PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

Deterministic sensitivity analysis

Figure 5: Tornado diagram with cabotegravir versus TDF/FTC (cabotegravir PAS price)

Abbreviations: ARV, antiretroviral; cabotegravir LA, cabotegravir long-acting; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; PAS, patient access scheme; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 6: Tornado diagram with cabotegravir versus no PrEP (cabotegravir PAS price)



Abbreviations: ARV, antiretroviral; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; PAS, patient access scheme; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

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Consultation on the draft guidance document – deadline for comments 5pm on Thursday 17 October 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	National AIDS Trust

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	ViiV Healthcare 29/04/24 - £20,000 – Core funding 26/06/24 - £64,000 – Contract for delivery of HIV Outcomes UK initiative
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**CAB-LA will help achieve the UK Government HIV Action Plan target of ending new HIV cases by 2030:** The UK Government's HIV Action Plan commits to ending new HIV transmissions by 2030. The HIV Action Plan and PrEP

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	roadmap (February 2024) acknowledge the pivotal role PrEP must play in ending new HIV cases by 2030 and the significant differences in PrEP need and uptake among marginalised communities. Both highlight that availability of PrEP beyond sexual health clinics and different modes of PrEP delivery, particularly long-acting PrEP, will improve uptake, acceptability and adherence. For many, especially gay and bisexual men and other men who have sex with men, daily PrEP pills are highly acceptable, well-tolerated and cost-effective for the NHS to administer. There are however significant inequities to PrEP access and social inequalities which mean that for many groups, oral PrEP options have not been able to bridge these divides. Particularly at a time when the latest UKHSA reporting highlights increased diagnoses and that delivery of the 2030 target is off course, introducing CAB-LA as an option for PrEP can enhance the reach of HIV prevention efforts, especially among high-risk populations who face barriers to oral PrEP that can include psychological issues such as stigma, difficultly accessing treatment, homelessness and domestic violence. CAB-LA will help to remove barriers and bridge a significant gap for communities underserved in the UK's HIV response. Data from the compassionate access program is crucial to consider, as it showcases real-world instances of patients who have already benefited from CAB-LA. This information also helps to demonstrates how the program could be delivered and expanded further if NICE recommends CAB-LA. It is essential that CAB-LA is made available to help ensure the UK meets its 2030 target.
2	**Population scope:** We understand NICE's position that further analysis using the whole population eligible for PrEP is necessary for the committee to make recommendations. We have concerns that this approach will overestimate the potential usage and cost of CAB-LA; leading to an inflated cost-effectiveness analysis. Submissions in the consultation period positions CAB-LA for those who cannot adhere to or tolerate daily oral PrEP, such as individuals with psychosocial issues, difficulty swallowing tablets, difficulty accessing treatment, lack of awareness or being homeless. The primary demand for injectable CAB-LA will come from a more defined group with unmet needs, for whom the long-acting injection is uniquely suited. Consideration of pricing the drug for a smaller, targeted population would better reflect its real-world application, improve its cost-effectiveness profile, and allow for more equitable access to those most in need. We agree with the British Association for Sexual Health and HIV in assessing that a sudden surge in oral PrEP users seeking to switch to injectable forms is unlikely. This pattern is consistent with what HIV services have observed in people living with HIV, where there has not been a significant demand for switching to injectable treatment. Therefore, we believe NICE can be reassured that a similar situation would likely arise if CAB-LA were licensed, with only a small proportion of patients requesting a switch from oral PrEP. We understand NICE's position that people who currently take oral PrEP exactly as prescribed

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	may not continue to take it the future and could enter the subpopulation of 'sub-optimal use' however recently updated PrEP guidelines (currently out for consultation) offers easier options for PrEP dosing, which should support with continued adherence to oral PrEP.
3	**Equality and addressing health inequalities:** We strongly disagree with the committee that inequality issues could not be addressed in the recommendations. Rejecting CAB-LA will disproportionately impact people with legally protected characteristics, such as Black and minority ethnic groups, trans and gender diverse communities, and those with disabilities, who are disproportionately affected by HIV and often face structural barriers to both healthcare and PrEP access. This decision also comes at a time of increasing HIV diagnoses and growing inequalities in the UK. Recently published data from UKHSA shows the steepest rise in HIV diagnoses among heterosexual men and women, particularly for minoritised groups. From 2022 to 2023, new HIV diagnoses among people of Black African ethnicity increased by 64% and diagnoses among women increased by 30% among women. CAB-LA has the potential to significantly benefit underserved groups, including women, homeless people, the prison population, trans and gender diverse communities, and others currently underserved by existing prevention options. These communities are known to be more likely to acquire HIV and to face barriers to healthcare and oral PrEP. Whilst the committee noted that issues related to differences in prevalence of a condition cannot be addressed in this technology appraisal, with increasing HIV diagnoses among key populations and continued barriers for accessing oral PrEP, we strongly believe that this is an equalities issue and has to be considered. Responding to the recent UKHSA data, the Minister for Public Health and Prevention said 'this data shows we have much more work to do and brings to light concerning inequalities in access to tests and treatments. I will be working across government to ensure that we work to stop HIV transmissions for good'. To action these commitments to tackle inequalities and 'stop HIV transmissions for good', NICE, NHSE and the UK Government should find a solution for the commissioning of CAB-LA which provides us the potential to prevent HIV transmissions and significantly benefit key populations that are underserved in HIV prevention options.

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4	**Underserved communities with unmet needs:** Research highlights that there are many individuals who face barriers such as stigma, homelessness, and domestic violence, which makes adherence to daily oral PrEP challenging. For example, for people who use drugs, whilst there hasn't been PrEP-use studies conducted, previous service evaluations in Scotland have demonstrated that delivering oral PrEP alongside oral opiate substitution therapy (OST) is feasible. With the recent shift to long-acting subcutaneous OST, the need for daily clinic visits has decreased, which could potentially lead to reduced adherence to oral PrEP. CAB-LA PrEP could eliminate the challenge of daily adherence for this group and may strengthen HIV prevention efforts in this population. 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. Long-acting injectable PrEP formulations offer similar advantages to injectable contraceptives, particularly by eliminating the need for daily dosing. The failure rate of oral contraceptives is often attributed to patient errors in pill-taking. Injectable contraceptives provide superior efficacy by removing the need to remember daily doses, which is especially beneficial for vulnerable women. This includes those without stable housing, experiencing domestic violence, living chaotic lives, working irregular shifts, or simply struggling to adhere to daily medication routines. The effectiveness of non-oral contraceptive methods is recognized in the Faculty of Sexual and Reproductive Healthcare guidelines, which recommend long-acting reversible contraceptives, including injectable options, as the preferred choice for all suitable women due to their superior efficacy and convenience. We share the British Association for Sexual Health and HIV's concerns that 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 underserved communities (including women and people who use drugs), the availability of a long-acting injectable like CAB-LA could significantly improve uptake and adherence, helping to close existing gaps in HIV prevention.
5	**CAB-LA administration costs:** We believe NICE's assessment that CAB-LA administration costs should be based on 1 hour of clinic time is too high. The process of administering the injection is straightforward and, as highlighted in clinical practice, can be efficiently integrated into routine appointments. The duration of an injection visit would likely be similar to other routine procedures like vaccinations or injectable treatments, requiring far less time than suggested in the draft guidance. Medium and large Sexual Health services that provide HIV care would likely reduce appointment times to 45 minutes or less. These centres

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	already have established pathways for administering injectable HIV treatments, and since only one injection is required for PrEP (compared to two for HIV treatment with Cabotegravir/Rilpivirine), the overall appointment time is likely to be under an hour. Furthermore, if a Band 5+ Nurse or Doctor administers the injection, which may take around 30 minutes, the patient could then be transferred to a Healthcare Assistant for post-injection observation and STI and blood-borne virus screening. CAB-LA's efficient administration could even reduce the overall clinical workload associated with PrEP as it could reduce time managing oral PrEP adherence challenges and ongoing monitoring of those with unmet needs.
6	**Cost-Effectiveness:** The draft guidance explores cost-effectiveness of CAB-LA and differing cost-effectiveness estimates from the company and the EAG. However, interpretations should not undervalue the long-term cost savings associated with preventing new HIV transmissions. PrEP can be initiated or discontinued based on an individual patient's needs, making it a more cost-effective approach over a lifetime compared to the long-term costs of lifelong medication and follow-up care that would be necessary if the individual were to later test positive for HIV. £220,000 is the average lifetime care costs for every new case of HIV. While the upfront costs of CAB-LA may be higher, the downstream savings related to reduced HIV transmission, and the associated healthcare costs, should not be overlooked. The cost-effectiveness model should also include broader societal benefits, such as reductions in productivity loss, stigma-related health impacts, and improvements in quality of life for communities at greater risk of contracting HIV.
7	**Generalisability of clinical trial data:** We recognise the committee decision that the clinical trial results were the best available evidence and could be used for decision making. CAB-LA has demonstrated superior efficacy across diverse geographic regions (including in sexual health services in low and middle income countries that have less resources than UK sexual health services) reinforcing its potential value in the UK. While the HPTN trials were not conducted in the UK, the National AIDS Trust agrees with clinical experts that the results are generalisable to the UK context, as the populations studied face similar risks and barriers. Due to the global nature of the HIV epidemic, the results of these trials should be relevant to populations in the UK, especially for those at high risk of acquiring HIV and for individuals who have migrated to the UK from countries with higher HIV prevalence. For instance, migrants in the UK face a greater risk of contracting HIV. Recent data from the UK Health Security Agency (UKHSA) indicates that in 2023, 53% of HIV diagnoses reported were among individuals who had been diagnosed abroad and migrants living in the UK are also at heightened risk of contracting compared to the UK general population.

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8	**Duration of HIV risk period:** We believe NICE's proposal to use a 10-year at-risk period for HIV acquisition in their economic model overestimates the likely duration of continuous PrEP use for most individuals. We believe the company's recommendation of a 5-year period is more aligned with real-world data and clinical practice. Given the dynamic nature of HIV risk, which can fluctuate due to changes in personal circumstances such as relationship status or behaviour, it is unlikely that most individuals will require PrEP for a full 10 years without interruption. In addition, the use of a 5-year period ensures a more accurate reflection of likely costs and benefits, avoiding the overestimation of both the time people remain at high risk and the costs associated with PrEP use over their lifetime. As clinical experts have indicated, five years captures a realistic at-risk period for many individuals, making it a more appropriate assumption for modelling HIV prevention strategies.
9	**Improved persistence with CAB-LA:** While the committee stated that the company's analyses should encompass the entire population eligible for CAB-LA - including those who currently adhere to oral PrEP as prescribed - 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. These people represent the communities most likely to seek CAB-LA in real-world settings.
10	**Adherence to TDF/FTC:** Whilst it is welcome that the committee concluded that it was appropriate to assume that adherence to TDF/FTC was lower for cis women compared with MSM and trans women, there is additional experiences from UK sexual health services and research into PrEP adherence challenges among women which could be considered. The 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.
11	**Implementation of CAB-LA injections:** We welcome the committee's acknowledgement of the importance of ensuring those who need PrEP have adequate access to any new PrEP options and the agreement with clinical experts that it would be useful if there were more routes available for people who need PrEP to access CAB-LA beyond sexual health services. Given the UK Government's PrEP Roadmap (February 2024) includes a commitment to improve access to PrEP in settings outside of sexual health services, working to facilitate access to CAB-LA outside of sexual health services (e.g GP surgeries or pharmacies) would be in line with Government commitments and support the delivery of the HIV Action Plan which is due to be updated in 2025. Expanding access to CAB-LA outside of sexual health services could also reduce administration costs and better serve underserved communities that may face barriers in going to sexual health services.

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association for Sexual Health and HIV (BASHH)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	[Insert disclosure here] [redacted] - I have no shares/investments in this or any other drug company. I can confirm I have not received financial or any other incentives personally from any pharmaceutical company within the past 12 months. I can declare I have no family or friends that have any direct/indirect interests related to a pharmaceutical company. BASHH – **ViiV Healthcare, sponsorship and exhibition stand at annual conference and support for conference scholarship programme.**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary** These consultation comments are submitted on behalf of the British Association for Sexual Health and HIV (BASHH) and have been informed by input from members of BASHH's HIV prevention working group and BASHH's HIV & Blood Borne Virus (BBV) Special Interest Group (SIG). BASHH is the lead professional representative body for specialist physicians in Genito-Urinary Medicine (GUM) managing sexually transmitted

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	infections (STIs) and HIV in the UK. It has a prime role in education and training, in determining, monitoring and maintaining standards of governance in sexual health and HIV care. BASHH also works to further the advancement of public health in relation to STIs, HIV and other sexual health problems and acts as a champion in promoting good sexual health and providing education to the public. BASHH is deeply disappointed by NICE's draft decision not to recommend Cabotegravir long-acting (CAB-LA) as a HIV prevention option. There is a chance afforded by CAB-LA to bridge inequities, especially in relation to Black women for whom the data shows the system is currently failing. We believe that NICE should fully approve CAB-LA as injectable PrEP and that doing so will play an important role in supporting the key commitment set out within the HIV Action Plan of reaching zero new HIV transmissions by 2030. This commitment is fundamentally linked to ensuring that all patients who may benefit from HIV prevention as PrEP are able to access this according to the needs of the individual. There is a backdrop of 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 CAB-LA for PrEP is important to improve equity of access and to begin to address these disparities in outcomes for key populations. While the recommendation from NICE does not directly restrict access to one group over another, we know that there are key populations (including those with single and multiple protected characteristics under the Equality Act) who are indirectly restricted from access to PrEP because of the unsuitability of oral PrEP for them. **Long-acting injectables provide a valuable treatment alternative for people where oral PrEP is not an option** A prominent factor which led to the approval of injectable antiretroviral therapy (ART) in 2022 was that injectables are beneficial for people who find daily tablets challenging or would prefer the flexibility associated with an injectable regimen. Clinical and community members both felt that injectable ART "could be an effective alternative when treatment adherence to daily oral regimen is affected either by side effects, when oral intake is impaired or when lifestyle interferes with following a daily regimen." BASHH argues that the same rationale also applies to patients who would benefit from CAB-LA PrEP. Current inequity in PrEP uptake is a significant barrier to the goal of reducing new HIV transmissions among vulnerable populations, of which women represent the second largest group in England. UKHSA 2023 data found that 28% of new HIV diagnoses first made in England were among women exposed through sex with men. GBMSM made up a similar proportion of new diagnoses (29%). Despite this, only 40.9% of heterosexual and bisexual women with a PrEP need, initiated or continued PrEP. This number was lower in non-white heterosexual and bisexual women. In comparison, 75.4% of GBMSM with a PrEP need initiated or continued PrEP. Clearly, further work is needed to engage women in PrEP services. A modelling study has estimated the efficacy of CAB-LA versus no PrEP to be 93-95% (Donnell D et al. Counterfactual estimation of efficacy against placebo for novel PrEP agents using external trial data: example of injectable cabotegravir and oral PrEP in women. J Int AIDS Soc. 2023 Jun;26(6):e26118.).

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	As with any intervention, choice and patient autonomy is paramount in order to support user acceptance and drive overall increases in uptake. This has been demonstrated through the benefits of offering a range of administration routes in contraception; there are parallels with PrEP. To only offer an oral treatment option in HIV prevention will hinder efforts to increase the acceptability, offer and uptake of PrEP, particularly amongst harder to reach, non-GBMSM populations. Previous experience with expansion of contraception options has demonstrated improved contraception coverage amongst women (McNicholas C, Madden T, Secura G, Peipert JF. The contraceptive CHOICE project round up: what we did and what we learned. Clin Obstet Gynecol. 2014 Dec;57(4):635-43. ; Ross J, Stover J. Use of modern contraception increases when more methods become available: analysis of evidence from 1982-2009. Glob Health Sci Pract. 2013 Jul 26;1(2):203-12.). This also helps to take account of the range of intersecting circumstances and factors, including social and cultural, that impact of the acceptability of certain regimens. It is also essential to recognise that there are sub-groups of more vulnerable populations who are at risk of HIV but who experience more difficulty adhering to oral PrEP. CAB-LA would therefore likely be particularly impactful in reducing HIV acquisition amongst these sub-groups, notably women (from HPTN 084 study), heterosexual men having sex with men, people in abusive situations, people living in houses in multiple occupation (HMO), and other groups, including those with higher levels of injecting drug use. There may also be significant repercussions regarding the stigma associated with using oral PrEP. Patients may not wish to have the tablets on their person or in the house for fear of their partner, family or household members discovering they are using PrEP. As domestic violence is a risk factor for HIV transmission, injectable PrEP would offer a safer alternative to preventing HIV transmission while protecting these patients from those close to them discovering they are using PrEP. A consultant in Genitourinary Medicine & HIV BASHH member submitted a case example demonstrating how intersecting factors impact on access to oral PrEP. *“I wish to highlight the experience of working in a service where a significant challenge has been the provision and acceptance of HIV prevention for heterosexual identifying men who have sex with men (HIMSM). These patients often are unable to engage with addressing preventive sexual health due to fear and self-stigma and often present significantly symptomatic. Many of these patients are in long term relationships with cis-women, so having PrEP tablets at home or on their person would raise suspicion. Within the last 2 years we have had at least one new diagnosis of HIV in a patient who had attended our service regularly for treatment of symptomatic bacterial STIs but was did not accept oral PrEP despite our best efforts. In addition to storage of medication being an issue, HIMSM can find negotiating condom use with their regular cis-female partners challenging as this would be likely to arouse suspicion in a relationship that is outwardly monogamous. Having the option to prescribe CAB-LA within our cohort, in addition to those who cannot tolerate oral options, has the potential to expand our ability to maintain the additional layers of confidentiality requested by our local population of HIMSM.”* In addition, CAB-LA provides an important treatment alternative for people with contraindications. There remains a challenging gap in HIV prophylaxis for instance in people whom TDF/FTC or TAF/FTC is contraindicated. Descovy PrEP (emtricitabine/tenofovir alafenamide, F/TAF), an alternative to tenofovir disoproxil-based PrEP (F/TDF), was commissioned in May 2023 for people with kidney or bone related

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	issues. However, Descovy is not licensed in cisgender women, compounding inequity for women with contraindications to F/TDF PrEP. **Improved adherence** BASHH further believes that CAB-LA will also improve non-stigma related adherence to PrEP, as supported by the following contribution from a BASHH member *"I would highlight that the failure rate of oral contraceptives is largely due to errors in pill-taking by patients and for that reason injectable contraceptives confer superior efficacy by eliminating the need to remember to take daily oral doses."* The benefits in efficacy of non-oral contraceptive preparations has been reflected in the Faculty of Sexual and Reproductive Health (FSRH) recommendation of LARC (long-acting reversible contraceptives) as a first-line contraception for all suitable women (which includes injectable preparations) in place of oral contraceptives, due to their superior efficacy and convenience for women. Long-acting injectable PrEP will confer the same advantages already demonstrated by injectable and long-acting contraceptives – most critically, avoiding the need to remember to take a dose every day. This has significant benefits for vulnerable people, including those with no fixed abode, who experience domestic violence, work changing shift patterns, or simply struggle to remember to take their pills. A member of the BASHH HIV & BBV SIG, commented, *"CAB-LA PrEP would remove the barrier of daily adherence for this group (who must adhere to daily PrEP for efficiency and to achieve benefit over risk) and could enhance combination HIV prevention in this target population."* Data from a large sexual health service in London found that 24% of individuals with newly diagnosed HIV had evidence of PrEP exposure with adherence challenges as the likely reason for PrEP failure. PrEP review appointments allow sexual health clinicians to identify PrEP adherence issues and provide relevant support. Therefore, routine PrEP follow-up care provides opportunities to identify individuals who may benefit from CAB-LA. Sexual health clinicians have a wealth of experience in identifying adherence issues with PrEP and ART and are well positioned to identify people who would benefit from CAB-LA. Previous attendance history can be a reliable indicator of the likelihood of attending 2 monthly injection appointments. There have been no studies or published real world evidence in people who inject drugs (PWID) as yet and previous service evaluation work in Scotland has shown oral PrEP delivery to be feasible alongside oral opiate substitution therapy (OST). There has been a shift however to long-acting subcutaneous OST and therefore reducing the need for daily attendance and therefore a potential for reduced adherence to oral PrEP. CAB-LA PrEP would remove the barrier of daily adherence for this group (who must adhere to daily PrEP for efficiency and to achieve benefit over risk) and could enhance combination HIV prevention in this target population. **Cost-effectiveness** 2023 data has shown a significant rise in HIV diagnoses in the population that would specifically, based on research, benefit from CAB-LA and therefore cost effectiveness must be calculated based on the increased incidence of HIV in this population.

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	Preventing access to PrEP within these subset of patients risks future acquisition of HIV and the costs associated with acquisition. As with most areas of medicine, it is inevitable that the costs of keeping some people free of HIV will be greater than others. Whilst BASHH understands that NICE must consider cost-effectiveness in its assessment, we strongly believe that the cost for CAB-LA is justified on the basis of HIV risk and/or complex medical and social issues. Further, in considering cost-effectiveness we are concerned that assessment based on the full indication for CAB-LA rather than likely population use puts up unnecessary barriers. Many of those who will access CAB-LA PrEP will be those who are currently not taking PrEP at all, for example. This is further supported by a contribution from a BASHH member, highlighting: *"I think it would be unlikely that there will be sudden surge in oral PrEP users requesting to start on injectables. This isn't something that we are seeing in people living with HIV so I think NICE should be reassured that a similar scenario is likely to occur if CAB-LA was licensed (i.e. a small proportion of patients requesting switch from oral PrEP)."* PrEP, including in injectable format, can be stopped or started according to an individual patient's need, which over a lifetime would be more cost effective than lifelong medication and follow-up expenditure required if an individual was to subsequently test positive for HIV, and experience the health complications that are associated with HIV acquisition. Where necessary, treatment costs could be managed through expert sexual health clinicians should having the opportunity to help identify patients who are particularly vulnerable to new transmission, on a case-by-case basis. Furthermore, following the approval of injectable ART in 2022, clinics did not see a surge in oral ART users requesting to start injectables. Instead, numbers of people on injectable ART has gradually increased over the years. The technology appraisal documents indicate that patients using CAB-LA PrEP are likely to require up to 60 minutes of clinician time (testing, administration, documentation). It is likely that sexual health services would reduce appointment times to 45 minutes or less. Centres of any size would organise their offering into high volume clinics e.g. offering clinics at certain times to increase throughput. Additionally, if a Band 5+ Nurse or Doctor administers the drug in 30 minutes, the patient could be transferred to a Healthcare Assistant for a period of observation and STI and BBV screening post injection. A large sexual health clinic in London manages continuation injections of CAB-LA (via compassionate use) in 20-minute nurse-led appointments with post injection waiting time in the waiting room (as standard of care with other injectable medicines given within GUM services). The External Assessment Group (EAG) argued that there was no evidence comparing CAB-LA to no PrEP. However, this would be challenging from an ethical perspective. Furthermore, data obtained from clinical trials with a 'No PrEP' arm would be limited, as trials would likely need to be stopped early due to superior efficacy in the intervention arm (as occurred in the PROUD Trial which had to be stopped early). A large sexual health clinic in London found that only 1-2% of their 25,000 PrEP users required consultant review due to intolerance or contraindications to PrEP. These represent a small and

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	clinically heterogeneous population of individuals for whom it would be extremely difficult to design a clinical trial to confirm that CAB-LA PrEP would be efficacious.

Insert extra rows as needed

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BHIV	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British HIV Association (BHIVA)

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We acknowledge that there may be some difficulty in clearly defining sub-populations for the purposes of the cost-effectiveness analysis. However, the proposed re-analysis risks obscuring the benefit in those who are most likely to benefit, by including all those on TDF/FTC. The relationship between adherence and effectiveness of oral PrEP needs careful consideration.

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	Evidence shows that people who take 4 pills of TDF/FTC per week have high levels of protection against acquiring HIV. This relationship with less than perfect adherence is best established in gay, bisexual and other men who have sex with men (GBMSM). However, a recent pooled analysis in cisgender women suggests that consistently maintained adherence of 4–6 pills a week is also associated with a high level of protection. Adherence is recognised as falling over time – well documented in women - but this "forgiveness" likely explains the high effectiveness of oral PrEP for many people. In the HPTN083 sub-study, drug levels consistent with at least 4 doses of oral PrEP were detected in 72.3% of samples overall, suggesting that approximately a third of the participants in that study would benefit from the use of Cabotegravir. In contrast in HPTN084, adherence measured by drug levels varied considerably over time, with results suggesting that 4 or fewer doses were taken per week in the majority of women. Assessing adherence is difficult without an objective measure and in the randomised studies reported adherence was substantially greater than that indicated by objective measures. Arguably, there is greater bias to report higher adherence in a clinical trial than in clinical practice. Nevertheless, self-report of consistently low levels of adherence (e.g. fewer than 4 pills a week) seems a reasonable way to determine those most likely to benefit from Cabotegravir in clinical practice.
2	It is welcome that the model includes lower estimates of adherence for cisgender women. There is also evidence of lower adherence in younger people (usually defined up to the age of 25 years), which might also be considered. (Allen E, Gordon A, Krakower D, Hsu K. HIV preexposure prophylaxis for adolescents and young adults. Curr Opin Pediatr. 2017 Aug;29(4):399-406). It is generally recognised across multiple areas of medicine, that adherence to interventions tends to be lower in young people and adolescents.
3	It is not appropriate to assume that all appointments for Cabotegravir PrEP will take 1 hour. This would likely be the maximum time needed for a few patients. While not published, informal feedback from clinics administering Cabotegravir PrEP under the compassionate access programme suggests that appointments take from 20-45 minutes (personal communication). Extrapolating from HIV treatment studies likely over-estimates the time needed since people with HIV require the preparation and administration of 2 injections, as well as assessment of potentially more complex HIV related needs and clinical concerns. The majority of those stable on PrEP will have blood tests taken but, as per standard clinical practice, take their own samples for STI testing. Drawing up and administration of an IM injection should be considered as taking a maximum of 5 minutes.
4	Sexual health clinicians clearly recognise individuals who would benefit from the use of cabotegravir as PrEP, e.g. demonstrated by use in the compassionate access programme. Clinicians report encounters with complex, vulnerable people where there are safeguarding concerns (personal communication). Cabotegravir represents an important opportunity to protect such individuals from HIV. If a further analysis of this intervention again finds that it exceeds the ICER, a conversation around how the NHS can deliver cabotegravir in these settings would be very welcome.
5	
6	

Insert extra rows as needed

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- Do not paste other tables into this table – type directly into the table.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UK Health Security Agency (UKHSA)

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Population included in the analysis:** We agree with the Committee's recommendation that the analysis should be extended to include the full population who could take cabotegravir in clinical practice, including those currently taking oral PrEP 'exactly as prescribed'. Forthcoming evidence from the 2023 RiiSH Survey suggests that willingness to use cabotegravir could be substantial amongst current oral PrEP users. RiiSH is an online cross-sectional survey of men and gender-diverse people who have sex with men in the UK recruited via social networking and dating applications. 963 respondents with negative or unknown HIV status completed the survey in 2023.

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	Of these, [redacted] would consider using a long-acting injectable lasting up to two months, compared to [redacted] of past users. To estimate the size of the population, we note that 2023 data is now available for the number of people continuing or using oral PrEP, as well as those with PrEP need who are not accessing oral PrEP (UKHSA, 2024). We caution these data likely underestimate total need. PrEP need is only estimated amongst individuals currently attending SHSs, meaning that need amongst people not attending SHSs is not accounted for. In addition, need is assessed on the basis of PrEP eligibility codes and other clinical or behavioural markers known to indicate a higher risk of HIV seroconversion. Need may therefore be underestimated if patients prefer not to disclose some behavioural markers. In practice, availability of cabotegravir could increase observed need and uptake amongst people attending SHSs as well as people who are not currently attending. Choice of methods has been shown in the context of contraception to promote uptake (Gray, 2006). If access to new treatments is conditioned on markers, this may also provide incentives for patients to disclose relevant behaviours (Calabrese, 2017). *Calabrese, Sarah K., Douglas S. Krakower, and Kenneth H. Mayer. 'Integrating HIV Preexposure Prophylaxis (PrEP) Into Routine Preventive Health Care to Avoid Exacerbating Disparities'. American Journal of Public Health 107, no. 12 (December 2017): 1883–89. https://doi.org/10.2105/AJPH.2017.304061.* *Gray, Andrew Lofts, Jennifer Ann Smit, Ntsiki Manzini, and Mags Beksinska. 'Systematic Review of Contraceptive Medicines "Does Choice Make a Difference?"' Reproductive Health & HIV Research Unit of the University of Witwatersrand, South Africa; World Health Organisation, 2006. https://indexmedicus.afro.who.int/iah/fulltext/ContraChoiceReview.pdf.* *UK Health Security Agency. 'Official Statistics for HIV Testing, PrEP, New HIV Diagnoses and Care Outcomes for People Accessing HIV Services: 2024 Report'. UK Health Security Agency, 2024. https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2024-report.*
2	**Baseline risk of HIV acquisition:** There are several limitations to the evidence currently used to inform both the company's and the EAG's preferred values for the baseline risk of HIV acquisition, as acknowledged by the Committee. There is additional, more relevant evidence that should be considered as an alternative. Baseline risk for eligible MSM and trans women: The 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. UKHSA's CD4 back-calculation model, which estimates HIV incidence amongst MSM, estimates that new infections fell 48% from 1,850 in 2015 to 970 in 2019 (UKHSA 2023). From 2019 onwards, estimated HIV incidence (based on the CD4 back-calculation model) amongst MSM has remained relatively stable, with an estimated 920 new infections in 2022 (UKHSA 2023). Modelling evidence calibrated to UKHSA data estimates that HIV incidence amongst MSM declined 77% between 2014 and 2022 (Cambiano 2024). The PrEP Impact Trial assessed HIV incidence amongst attendees at sexual health services in England between 2017 and 2020 (Sullivan 2023). 157 services participated, representing more than 81% of sexual health service (SHS) activity in 2019. The trial estimated HIV incidence

amongst both trial participants taking oral PrEP and non-participating attendees. Given the scale and design of the trial, we consider these estimates provide a robust estimate of current incidence rates amongst MSM attending SHSs which can be disaggregated by PrEP usage.

The estimate we recommend for the eligible population of MSM and trans women not taking oral PrEP is 0.95/100 person-years. This is the incidence estimated in the trial for the overall population of MSM attendees at SHSs who were HIV negative (defined as a negative HIV test at their visit after trial recruitment had begun, or otherwise in the last 12 months) and did not participate in the trial. MSM attendees who did not have a negative HIV test were not included as this could bias results by including individuals with existing undiagnosed HIV. An estimate is also available for a higher risk subset of this population, categorised on the basis of markers including a recent rectal bacterial STI diagnosis, use of HIV PrEP or prophylaxis, and being a sexual contact of someone diagnosed with HIV or syphilis. Given that people can be eligible for PrEP without any of these markers, using the estimate for a higher risk subset only could bias results. However, the estimate for the higher risk subset is comparatively lower than for the broader population, at 0.74/100 person years. Rates of rectal gonorrhoea increased substantially amongst MSM attending SHSs between 2011 and 2018, whilst HIV incidence decreased, indicating that rectal STIs are now less strongly correlated with HIV incidence on a population level (Donnell 2020).

The estimate we recommend for the eligible population of MSM and trans women eligible for cabotegravir and currently taking oral PrEP is 0.13/100 person years, the incidence estimated for MSM trial participants. This direct evidence will be more reliable than the currently proposed approach of adjusting incidence amongst MSM not currently taking oral PrEP using evidence from trials conducted in other settings and systematic review evidence.

Baseline risk for eligible cisgender women: There is less evidence and significantly more uncertainty about the baseline risk of HIV transmission for cisgender women. It was not possible to estimate HIV incidence amongst women in the PrEP Impact Trial due to the small number of seroconversions observed (Sullivan, 2023). We have concerns about the company's preferred estimates, which use trial data from Sub-Saharan Africa to approximate risk amongst women living in the UK. Epidemiology, healthcare delivery and access to services vary markedly between these contexts.

The most credible estimate of incidence in eligible cisgender women that we are aware of is from a study of SHS attendees between 2009-2013 (Aghaizu, 2018). Incidence amongst black African heterosexuals was estimated to be 0.19/100 person-years in 2013. The number of new HIV diagnoses amongst women first diagnosed in the UK was [redacted] in 2023 compared to [redacted] in 2015 (unpublished UKHSA analysis, earlier data is not available). We note that incidence amongst MSM in the same study was 1.46/100 person years. This illustrates that the incidence rate from eligible MSM cannot be used to infer that of cisgender women.

Aghaizu, Adamma, Jennifer Tosswill, Daniela De Angelis, Helen Ward, Gwenda Hughes, Gary Murphy, and Valerie Delpech. 'HIV Incidence among Sexual Health Clinic Attendees in England: First Estimates for Black African Heterosexuals Using a Biomarker, 2009-2013'. Edited by Dimitrios Paraskevis. PLOS ONE 13, no. 6 (20 June 2018): e0197939. https://doi.org/10.1371/journal.pone.0197939.

Cambiano, Valentina, Alec Miners, Fiona C Lampe, Sheena McCormack, O Noel Gill, Graham Hart, Kevin A Fenton, et al. 'The Effect of Combination Prevention Strategies on HIV Incidence among Gay and Bisexual Men Who Have Sex with Men in the UK: A Model-Based Analysis'. The Lancet HIV 10, no. 11 (November 2023): e713–22. https://doi.org/10.1016/S2352-3018(23)00204-7.

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	Donnell, Deborah, Kidist Zewdie, Natasha Ratna, Veronica Miller, John Michael Saunders, O Noel Gill, Valerie Delpech, and Hamish Mohammed. 'Association between Rectal Gonorrhoea and HIV Incidence in Men Who Have Sex with Men: A Meta-Analysis'. Sexually Transmitted Infections 98, no. 7 (November 2022): 492–96. https://doi.org/10.1136/sextrans-2021-055254. *Sullivan, Ann K, John Saunders, Monica Desai, Andrea Cartier, Holly D Mitchell, Sajjida Jaffer, Dana Ogaz, et al. 'HIV Pre-Exposure Prophylaxis and Its Implementation in the PrEP Impact Trial in England: A Pragmatic Health Technology Assessment'. The Lancet HIV 10, no. 12 (December 2023): e790–806. https://doi.org/10.1016/S2352-3018(23)00256-4.* *UK Health Security Agency. 'HIV Action Plan Monitoring and Evaluation Framework 2023 Report'. UK Health Security Agency, 2023. https://www.gov.uk/government/publications/hiv-monitoring-and-evaluation-framework/hiv-action-plan-monitoring-and-evaluation-framework-2023-report.*
3	**Starting age of people in the model:** There is limited data available on the age at which people initiate PrEP. 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). However, we note that the 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). In addition, there is evidence that individuals are most likely to have multiple sexual partners between the ages of 16 and 24. Data from the National Survey of Sexual Attitudes and Lifestyles (NATSAL) 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). We caveat that this evidence relates to heterosexual sex. *Mercer, Catherine H, Clare Tanton, Philip Prah, Bob Erens, Pam Sonnenberg, Soazig Clifton, Wendy Macdowall, et al. 'Changes in Sexual Attitudes and Lifestyles in Britain through the Life Course and over Time: Findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal)'. The Lancet 382, no. 9907 (November 2013): 1781–94. https://doi.org/10.1016/S0140-6736(13)62035-8.* *UK Health Security Agency. 'Official Statistics for HIV Testing, PrEP, New HIV Diagnoses and Care Outcomes for People Accessing HIV Services: 2024 Report'. UK Health Security Agency, 2024. https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2024-report.*

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Dr Michael Brady Consultant in HIV and Sexual Health, Kings College Hospital, London

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Dr Michael Brady

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	I do not agree with the statement that there "may be difficulties in identifying individuals who cannot have or tolerate oral PrEP". Clinicians who specialise in sexual health and HIV prevention have considerable experience in identifying and supporting those who, for whatever reason, struggle to take oral PrEP. We are expert in identifying those who have poor adherence and / or are not tolerating medication. We 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. I have no doubt that

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	sexual health clinicians in specialist services would easily be able to identify those who would most benefit from injectable PrEP. I note that the committee felt that "…people who do not take oral PrEP exactly as prescribed cannot be identified using defined characteristics. For these reasons, this group is a difficult subpopulation to define in clinical practice." As above – I do not agree with this statement. Whilst there are no objective measures of adherence used in routine clinical practice (as would be used in a clinical trial), sexual health and HIV clinicians are experts at discussing adherence and identifying those who struggle to take medication as prescribed. It is a fundamental part of our standard clinical care. I have no doubt that clinicians would be able to identify those who are struggling with adherence, especially in the context of have an injectable PrEP option to offer people as an alternative. There is already experience amongst sexual health clinicians in identifying individuals who have complex medical problems which prevent them from taking oral PrEP and in supporting them, through compassionate access, to use cabotegravir PrEP. Ongoing review of these patients has shown the success of cabotegravir PrEP in individuals at high risk of HIV acquisition for whom oral PrEP is not an option.
2	I do not agree with the statement that "people who cannot take oral PrEP were not included in the key clinical trials". Whilst this was not a specific inclusion criterion for the HPTN083 and HPTN084 trials, it is clear from the adherence data and the inferior efficacy of oral PrEP when compared to cabotegravir that people who struggle to take oral PrEP were included in the trials. For example, in HPTN083 adherence to TDF/FTC clearly reduced over time. At week 4, 18% of participants in the TDF/FTC arm had drug levels lower than needed to protect from HIV acquisition (poor adherence) and this increased to 33.3% having suboptimal drug levels by week 81. https://www.nejm.org/doi/full/10.1056/NEJMoa2101016
3	I note that the EAG decided to use a 10-year period for people being at risk of HIV and I note (and recall) the discussions we had about this. I think the selection of a 10-year period for people being at risk of HIV acquisition is too long, does not fit with our clinical experience and is not supported by any data. I have been prescribing PrEP for 10 years for hundreds, if not thousands, of people and can only think of one person who is still on PrEP for that length of time. Whilst I accept that people may be accessing PrEP elsewhere, I think the 'cautious' selection of a 10-year risk period is not correct. I agree, as noted, that people move in and out of risk periods for HIV acquisition but think a 5-year period of presumed risk is more accurate and closer to our clinical and 'real life' experience.
4	I agree with the committee's decision that it is appropriate to allow some people to transition from cabotegravir to oral TDF/FTC. As I said in the meeting – although cabotegravir injectable PrEP may be the most acceptable PrEP for some people there will be many for whom oral TDF/FTC is not *absolutely* contraindicated and, therefore, once engaged in services and if for some reason an individual wants to stop cabotegravir there would be a proportion that transition to oral TDF/FTC. I think the proportion estimated by the company is a reasonable estimate of the numbers who might do this. I do not agree with the committee when they say that the proportion "is unlikely to be as high as the company's assumption".
5	I do not agree with the EAG's assumption that "persistence with cabotegravir will be equal to oral PrEP". I think this fails to take into account the increased acceptability of a novel injectable form of PrEP in cabotegravir. When there is only one option (oral TDF/FTC) people will either not engage with it or struggle with adherence if it is not the most acceptable form of PrEP for them. By definition, individuals who are able to access cabotegravir injectable PrEP will be taking a form of PrEP that is more suited to them and, therefore, adherence (as was demonstrated in the HPTN083 and HPTN 084 trials) and persistence will be better. In a similar way we have seen

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	improved adherence and persistence with treatment for those living with HIV when we've been able to increase options and choice and better tailor therapy to an individual's needs. To assume that adherence and persistence to injectable PrEP will be the same as oral PrEP is to ignore the acceptability impact of providing greater choice of PrEP options. I agree with the statement that "The committee concluded that there would likely be an improvement in persistence with cabotegravir but there was uncertainty around the percentage improvement" but I would encourage you to not underestimate this impact.
6	I do not agree with the decision to set the likely administration appointment time of one hour for cabotegravir injectable PrEP and would encourage the committee to reconsider this. I can think of no other clinical intervention in sexual health or HIV services that routinely requires an appointment of an hour and I think this assumption considerably over states the time required for a cabotegravir PrEP appointment. Services who already have some experience of providing cabotegravir PrEP through compassionate access report that a 30-minute appointment is appropriate. Similarly, experience in our clinic of providing injectable therapy for people living with HIV is that this can be managed in a nurse-led clinic with a 30-minute appointment. An appointment time of 30 minutes 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 – which is a service model that is already very established in many clinics and is becoming increasingly common across the country..
7	Whilst noting some of the limitations of the available data I agree with committee's decision to use the HIV disutility index of -0.11
8	I relation to the equalities and health inequity considerations I am concerned that the initial outcome of not recommending cabotegravir injectable PrEP could widen and perpetuate existing health inequalities for some groups in terms of their access to PrEP and our ability to support them to prevent HIV acquisition. As has been highlighted in this process and noted in the EIA "HIV disproportionately affects people of Black African family background" and that "HIV is more prevalent in people of certain sexual orientations such as gay or bisexual men." Our clinical experience in the UK, which is supported by data from the clinical trials is that heterosexual men and women and, especially, black African women are significantly underrepresented in cohorts taking PrEP and face specific barriers to access and uptake of PrEP. The clinical trial data in black African women demonstrating superiority of cabotegravir PrEP over oral TDF/FTC is compelling an important. To ignore this and / or not facilitate access to greater PrEP options through provision of cabotegravir injectable PrEP is to fail to address the existing discrimination and inequalities in PrEP access – especially in relation to cisgender women and those from black African and other minority ethnic communities. The most recently published data from the UKHSA (October 2024) has demonstrated the even greater need for a range of PrEP options to better meet the needs of already underserved populations. The data show an increase in HIV diagnoses and greater inequalities as this disproportionally affects heterosexuals and those from minority ethnic groups. https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2024-report The majority of PrEP users in the UK are gay, bisexual and other men who have sex with men (GBMSM) whilst other groups who have similar risks of HIV acquisition – especially black African women – remain at risk because of both the lack of an acceptable PrEP option and our failure to engage these communities in PrEP services. HPTN084 clearly demonstrates the superiority of cabotegravir PrEP for these groups and these data are certainly transferrable to the UK setting, I would encourage the committee to further consider the equalities impact and potential exacerbation of existing inequalities should injectable PrEP not be available for those who would benefit from it.

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9	Finally – I would recommend the committee consider a range of recently published data that demonstrate the significant impact that injectable PrEP can have in addressing inequalities in access and uptake and supporting better adherence and persistence when compared to currently available oral PrEP with TDF/FTC. For example: Systematic review of the values and preferences regarding the use of injectable pre-exposure prophylaxis to prevent HIV acquisition. Lorenzetti L, Dinh N, van der Straten A, Fonner V, Ridgeway K, Rodolph M, Schaefer R, Schmidt HA, Baggaley R. J Int AIDS Soc. 2023 Jul;26 Suppl 2(Suppl 2):e26107. doi: 10.1002/jia2.26107. PMID: 37439057 Willingness and preferences for long-acting injectable PrEP among US men who have sex with men: a discrete choice experiment. Cole SW, Glick JL, Campoamor NB, Sanchez TH, Sarkar S, Vannappagari V, Rinehart A, Rawlings K, Sullivan PS, Bridges JFP. BMJ Open. 2024 Apr 22;14(4):e083837. doi: 10.1136/bmjopen-2023-083837. PMID: 38653510 Provider Factors Likely to Impact Access and Uptake of Long-Acting Injectable Cabotegravir for Transgender Women in the United States: Results of a Qualitative Study. Rael CT, Das D, Porter J, Lopez-Ríos J, Abascal E, Dolezal C, Vaughn MP, Giffenig P, Lopez JM, Stonbraker S, Sun C, Velasco RA, Bitterfeld L, Bockting WO, Bauermeister J. J Assoc Nurses AIDS Care. 2024 Sep-Oct 01;35(5):437-449. doi: 10.1097/JNC.0000000000000488. Epub 2024 Aug 13. Assessing Preferences for Long-Acting Injectable Pre-Exposure Prophylaxis Among Young Adult Sexual Minority Men and Transgender Women. Weeden T, Garofalo R, Johnson AK, Schnall R, Cervantes M, Scherr T, Kuhns LM. Acad Pediatr. 2024 Sep-Oct;24(7):1110-1115. doi: 10.1016/j.acap.2024.04.005. Epub 2024 Apr 15. PMID: 38631476 Clinical Trial. Perspectives on long-acting formulations of pre-exposure prophylaxis (PrEP) among men who have sex with men who are non-adherent to daily oral PrEP in the United States. Rogers BG, Chan PA, Sutten-Coats C, Zanowick-Marr A, Patel RR, Mena L, Goedel WC, Chu C, Silva E, Galipeau D, Arnold T, Gomillia C, Curoe K, Villalobos J, Underwood A, Sosnowy C, Nunn AS. BMC Public Health. 2023 Aug 28;23(1):1643. doi: 10.1186/s12889-023-16382-4. PMID: 37641018 Willingness to use and preferences for long-acting injectable PrEP among sexual and gender minority populations in the southern United States, 2021-2022: cross-sectional study. Schoenberg P, Edwards OW, Merrill L, Martinez CA, Stephenson R, Sullivan PS, Jones J. J Int AIDS Soc. 2023 Mar;26(3):e26077. doi: 10.1002/jia2.26077. PMID: 36951057 Preferential Initiation of Long-Acting Injectable Versus Oral HIV Pre-Exposure Prophylaxis Among Women Who Inject Drugs.

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Rachael Jones, Consultant Physician HIV/GUM, NHSE HIV CRG

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Small grant (£10 000) received to my local institution (10 Hammersmith Broadway, Chelsea and Westminster Hospital) from Gilead Sciences for patient education materials in the last 12 months.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none
Name of commentator person completing form:	Rachael Jones

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Many thanks for the opportunity to comment on the NICE draft guidance following the first round of discussion on the use of cabotegravir PrEP in England. I am concerned that the initial outcome of not recommending cabotegravir will drive health inequity and deny access to those most in need, thus leaving them at risk of HIV acquisition, hence I would argue that the provisional recommendations are not a sound and suitable basis for guidance to the NHS. The current recommendation risks failing to promote equality of opportunity and the elimination of discrimination. It also fails to foster good relations between people with particular protected characteristics as it will deny access to cohorts of individuals for whom current PrEP options are not appropriate in whom cabotegravir has been proven to be superior e.g. cis-women.

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	I do understand, however, that NICE feel the evidence presented in the initial model and discussion did not cover everyone who could benefit from cabotegravir in clinical practice as the company positioned cabotegravir for a narrower population. Given the recent UKHSA 2023 data outlining the rise in HIV rates within the UK (6008 new HIV diagnoses, an increase of 51% from 2022) the need for greater PrEP access and modalities is critical. The rise has disproportionately affected ethnic minority groups, leading to UKHSA to state that 'further provision of services is needed that are accessible to diverse key populations and culturally competent'. https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2024-report These data also show that the majority of PrEP users continue to be gay or bisexual men who have sex with men (GBMSM). PrEP uptake in other at-risk cohorts remains low and PrEP inequity has increased with negative outcomes for some groups, particularly Black women as discussed in the initial meeting. The HPTN data serve to demonstrate the success of cabotegravir in all groups with much of the failure of oral therapy being linked to poor adherence. This has been seen in more recent studies of the injectable PrEP agent lenacapavir vs oral therapy. Twice-Yearly **Lenacapavir** or Daily F/TAF for HIV Prevention in Cisgender Women. Bekker LG,et al; PURPOSE 1 Study Team.N Engl J Med. 2024 Jul 24. Io90 As detailed in my previous submission, alternative PrEP options serve to improve PrEP access and uptake and provide an alternative for individuals for whom standard of care PrEP is not appropriate or inferior. Without a broader range of PrEP options, we will continue to neglect the most vulnerable members of our society and fail to meet the goals of the HIV Action Plan. .
2	Since the initial round of evidence collection, multiple studies have been published to demonstrate that long acting injectable PrEP would increase PrEP uptake and persistence in those who have been 'left behind' by current PrEP agents and studies e.g. cis-women, people who inject drugs, those who struggle with adherence, the taking of oral medication or those in whom the current standard of care agents are contraindicated. Preferential Initiation of Long-Acting Injectable Versus Oral HIV Pre-Exposure Prophylaxis Among Women Who Inject Drugs. Roth AM, Bartholomew TS, Ward KM, Groves A, Mazzella S, Bellamy S, Amico KR, Carrico AW, Ironson G, Krakower D. Clin Infect Dis. 2024 Sep 30:ciae450. doi: 10.1093/cid/ciae450. Online ahead of print. PMID: 39347705 Health impact, budget impact, and price threshold for cost-effectiveness of lenacapavir for HIV pre-exposure prophylaxis in eastern and southern Africa: a modelling analysis. Wu L, Kaftan D, Wittenauer R, Arrouzet C, Patel N, Saravis AL, Pfau B, Mudimu E, Bershteyn A, Sharma M. Lancet HIV. 2024 Sep 20:S2352-3018(24)00239-X. doi: 10.1016/S2352-3018(24)00239-X. Online ahead of print. PMID: 39312933 Provider Factors Likely to Impact Access and Uptake of Long-Acting Injectable Cabotegravir for Transgender Women in the United States: Results of a Qualitative Study.

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	Who prefers what? Correlates of preferences for next-generation HIV prevention products among a national U.S. sample of young men who have sex with men. Biello KB, Valente PK, da Silva DT, Lin W, Drab R, Hightow-Weidman L, Mayer KH, Bauermeister JA; iTech Team. J Int AIDS Soc. 2023 Jul;26 Suppl 2(Suppl 2):e26096. doi: 10.1002/jia2.26096. PMID: 37439061 Systematic review of the values and preferences regarding the use of injectable pre-exposure prophylaxis to prevent HIV acquisition. Lorenzetti L, Dinh N, van der Straten A, Fonner V, Ridgeway K, Rodolph M, Schaefer R, Schmidt HA, Baggaley R. J Int AIDS Soc. 2023 Jul;26 Suppl 2(Suppl 2):e26107. doi: 10.1002/jia2.26107. PMID: 37439057 Barriers and facilitators to HIV pre-exposure prophylaxis for cisgender and transgender women in the UK. Whelan I, Strachan S, Apea V, Orkin C, Paparini S. Lancet HIV. 2023 Jul;10(7):e472-e481. doi: 10.1016/S2352-3018(23)00080-2. Epub 2023 Jun 1. PMID: 37271160 Exploring preferences and decision-making about long-acting injectable HIV pre-exposure prophylaxis (PrEP) among young sexual minority men 17-24 years old. John SA, Zapata JP, Dang M, Pleuhs B, O'Neil A, Hirshfield S, Walsh JL, Petroll AE, Quinn KG. Sci Rep. 2023 Mar 29;13(1):5116. doi: 10.1038/s41598-023-32014-8. PMID: 36991027 Willingness to use and preferences for long-acting injectable PrEP among sexual and gender minority populations in the southern United States, 2021-2022: cross-sectional study. Schoenberg P, Edwards OW, Merrill L, Martinez CA, Stephenson R, Sullivan PS, Jones J. J Int AIDS Soc. 2023 Mar;26(3):e26077. doi: 10.1002/jia2.26077. PMID: 36951057 . Brief Report: Refusal of Daily Oral PrEP: Implementation Considerations and Reported Likelihood of Using Various HIV Prophylaxis Products in a Diverse Sample of MSM. Mansergh G, Kota KK, Carnes N, Gelaude D. J Acquir Immune Defic Syndr. 2023 Mar 1;92(3):212-216. doi: 10.1097/QAI.0000000000003134. PMID: 36442153
3	In section 3.2, NICE have stated that there may be difficulties in identifying individuals who cannot have or tolerate oral PrEP. I would argue that this is not the case. Clinicians have over a decade of experience in managing PrEP, we are skilled in recognising those in whom PrEP would be of benefit and in ascertaining which modality of PrEP would be most appropriate throughout the period of PrEP use. We ask detailed questions re adherence and recognise those in whom risk may be greater. Engagement in clinical care is a surrogate marker for persistence and hence we are well placed to identify individuals in whom alternative PrEP options would be of benefit. For PrEP-users with medical issues which prohibit use of the current standard of care agents, many of us have applied to ViiV for compassionate access to cabotegravir. While this cohort of current UK cabotegravir users remains small (less than 20 currently), a review of the data has demonstrated the success of cabotegravir in this population at high risk of HIV acquisition.
4	In section 3.3, NICE have stated that it was concerned that people who currently take oral PrEP as prescribed may not continue in future and could enter the sub-population of 'sub-optimal use' in order to access

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	cabotegravir. I would argue against this comment. It is highly unlikely that individuals would put themselves at risk in such a way having already engaged in PrEP in order to reduce the likelihood of HIV acquisition. While an excellent option for some, with impressive clinical trial results, cabotegravir will not be the PrEP agent of choice for the majority of PrEP users due to the need to attend clinic on a two monthly basis. While we should not extrapolate from the HIV field, it is important to note that the same concerns were raised with the introduction of injectable antiretroviral therapy. Currently, less than 2% of people with HIV on antiretroviral therapy have switched to injectables. While there are other caveats which restrict injectable use for HIV treatment, anecdotally, the main driver in reducing uptake is having to attend clinic more frequently.
5	In 3.4, I note that the EAG comment that people who cannot take oral PrEP are not included in the HPTN studies. Again, I would argue that this is not the case. While I agree that they are not identified at baseline (impossible to do in a PrEP naïve cohort), these individuals are included and they are those that will have struggled with adherence to TDF/FTC leading to its inferiority in these studies.
6	The guidance consultation has highlighted in section 3.4, that there is no clinical trial data to compare cabotegravir with no PrEP. Given this is has been deemd unethical for over a decade, the company have extrapolated data from other studies. It may be useful to look at the cohort data of cabotegravir use in the UK which has demonstrated that having cabotegravir available via the compassionate programme has led to the availability of a successful prevention strategy in individuals with no other PrEP options.
7	In section 3.9, the guidance discusses HIV incidence rates, I would agree with the 3.9 per 100 person years but would highlight that incidence studies are lacking and these data are from GBMSM cohorts.
8	I note in section 3.10 that the EAG prefer to use the at-risk HIV period of 10 years. As discussed at the initial meeting, I think this is too long and not fitting with clinical experience. There are no studies supporting the 10 year figure, most PrEP persistence studies outside of trial settings do not even meet the five year figure which was suggested by the company initially. Retention in care outcomes for HIV pre-exposure prophylaxis implementation programmes among men who have sex with men in three US cities - Chan - 2016 - Journal of the International AIDS Society Determinants of Pre-Exposure Prophylaxis (Prep) Persistence in a High-Risk Population in Central Florida - Jonathan Keyes, Eloisa Catherine Crouse, Edwin DeJesus, Charlotte-Paige Rolle, 2021 Persistence on HIV preexposure prophylaxis medication over a 2-year period among a national sample of 7148 PrEP users, United States, 2015 to 2017 - Coy - 2019 - Journal of the International AIDS Society - Wiley Online Library
9	When discussing transitioning to TDF/FTC on cessation of cabotegravir, there were concerns regarding the number of individuals able to transition as detailed in section 3.11. As detailed, there will be a population who cannot transition to TDF/FTC given clinical contraindications but other PrEP options are likely to be available in future for this cohort. As discussed, should cabotegravir become available, data show that it is likely to improve access to individuals in whom oral PrEP options are not preferred due to issues of stigma, violence etc Having been established on cabotegravir PrEP, circumstances may change in order for them to use TDF/FTC on cabotegravir cessation.

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10	The committee concluded in section 3.13 that it was appropriate to assume that adherence to TDF/FTC was lower for cis-women. Since our initial meeting, lower adherence rates in cis-women has been observed further in the Purpose-1 Lenacapavir PrEP study.
11	In section 3.16, the committee has concluded that administration costs should be based on one hour of clinic time. With experience, it is likely that this timing will be significantly shorter. Clinics with experience of delivering cabotegravir PrEP have reported 30 minute appointments to be sufficient, especially if the PrEP user has already undergone online sexual health screening. It should also be noted that the company have data (presented at CROI 2024) on the use of 'ultra-long' cabotegravir where the agent may be administered four-monthly (as opposed to two-monthly) thus further reducing future costs.
12	I agree with the use of the greater disutility index of -0.11 in section 3.17.
13	I look forward to reviewing the updated model and hope that NICE will recognise the need for cabotegravir in reducing health inequity and the provision of a suitable PrEP option for those individuals in whom the current standard of care options are inferior.

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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 17 October 2024. Please submit via NICE Docs.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	UKHSA
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

There is additional relevant evidence available on the below topics:

Population included in the analysis:

We agree with the Committee's recommendation that the analysis should be extended to include the full population who could take cabotegravir in clinical practice, including those currently taking oral PrEP 'exactly as prescribed'. Forthcoming evidence from the 2023 RiiSH Survey suggests that willingness to use cabotegravir could be substantial amongst current oral PrEP users. RiiSH is an online cross-sectional survey of men and gender-diverse people who have sex with men in the UK recruited via social networking and dating applications. 963 respondents with negative or unknown HIV status completed the survey in 2023. Of these, [redacted] would consider using a long-acting injectable lasting up to two months, compared to [redacted] of past users.

To estimate the size of the population, we note that 2023 data is now available for the number of people continuing or using oral PrEP, as well as those with PrEP need who are not accessing oral PrEP (UKHSA, 2024). We caution these data likely underestimate total need. PrEP need is only estimated amongst individuals currently attending SHSs, meaning that need amongst people not attending SHSs is not accounted for. In addition, need is assessed on the basis of PrEP eligibility codes and other clinical or behavioural markers known to indicate a higher risk of HIV seroconversion. Need may therefore be underestimated if patients prefer not to disclose some behavioural markers.

In practice, availability of cabotegravir could increase observed need and uptake amongst people attending SHSs as well as people who are not currently attending. Choice of methods has been shown in the context of contraception to promote uptake (Gray, 2006). If access to new treatments is conditioned on markers, this may also provide incentives for patients to disclose relevant behaviours (Calabrese, 2017).

Calabrese, Sarah K., Douglas S. Krakower, and Kenneth H. Mayer. 'Integrating HIV Preexposure Prophylaxis (PrEP) Into Routine Preventive Health Care to Avoid Exacerbating Disparities'. American Journal of Public Health 107, no. 12 (December 2017): 1883–89. https://doi.org/10.2105/AJPH.2017.304061.

Gray, Andrew Lofts, Jennifer Ann Smit, Ntsiki Manzini, and Mags Beksinska. 'Systematic Review of Contraceptive Medicines "Does Choice Make a Difference?"' Reproductive Health & HIV Research Unit of the University of Witwatersrand, South Africa; World Health Organisation, 2006. https://indexmedicus.afro.who.int/iah/fulltext/ContraChoiceReview.pdf.

UK Health Security Agency. 'Official Statistics for HIV Testing, PrEP, New HIV Diagnoses and Care Outcomes for People Accessing HIV Services: 2024 Report'. UK Health Security Agency, 2024. https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2024-report.

Baseline risk of HIV acquisition:

There are several limitations to the evidence currently used to inform both the company's and the EAG's preferred values for the baseline risk of HIV acquisition, as acknowledged by the Committee. There is additional, more relevant evidence that should be considered as an alternative.

Baseline risk for eligible MSM and trans women: The 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. UKHSA's CD4 back-calculation model, which estimates HIV incidence amongst MSM, estimates that new infections fell 48% from 1,850 in 2015 to 970 in 2019 (UKHSA 2023). From 2019 onwards, estimated HIV incidence (based on the CD4 back-calculation model) amongst MSM has remained relatively stable, with an estimated 920 new infections in 2022 (UKHSA 2023). Modelling evidence calibrated to UKHSA data estimates that HIV incidence amongst MSM declined 77% between 2014 and 2022 (Cambiano 2024).

The PrEP Impact Trial assessed HIV incidence amongst attendees at sexual health services in England between 2017 and 2020 (Sullivan 2023). 157 services participated, representing more than 81% of sexual health service (SHS) activity in 2019. The trial estimated HIV incidence amongst both trial participants taking oral PrEP and non-participating attendees. Given the scale and design of the trial, we consider these estimates provide a robust estimate of current incidence rates amongst MSM attending SHSs which can be disaggregated by PrEP usage.

The estimate we recommend for the eligible population of MSM and trans women not taking oral PrEP is 0.95/100 person-years. This is the incidence estimated in the trial for the overall population of MSM attendees at SHSs who were HIV negative (defined as a negative HIV test at their visit after trial recruitment had begun, or otherwise in the last 12 months) and did not participate in the trial. MSM attendees who did not have a negative HIV test were not included as this could bias results by including individuals with existing undiagnosed HIV. An estimate is also available for a higher risk subset of this population, categorised on the basis of markers including a recent rectal bacterial STI diagnosis, use of HIV PrEP or prophylaxis, and being a sexual contact of someone diagnosed with HIV or syphilis. Given that people can be eligible for PrEP without any of these markers, using the estimate for a higher risk subset only could bias results. However, the estimate for the higher risk subset is comparatively lower than for the broader population, at 0.74/100 person years. Rates of rectal gonorrhoea increased substantially amongst MSM attending SHSs between 2011 and 2018, whilst HIV incidence decreased, indicating that rectal STIs are now less strongly correlated with HIV incidence on a population level (Donnell 2020).

The estimate we recommend for the eligible population of MSM and trans women eligible for cabotegravir and currently taking oral PrEP is 0.13/100 person years, the incidence estimated for MSM trial participants. This direct evidence will be more reliable than the currently proposed approach of adjusting incidence amongst MSM not currently taking oral PrEP using evidence from trials conducted in other settings and systematic review evidence.

Baseline risk for eligible cisgender women: There is less evidence and significantly more uncertainty about the baseline risk of HIV transmission for cisgender women. It was not possible to estimate HIV incidence amongst women in the PrEP Impact Trial due to the small number of seroconversions observed (Sullivan, 2023). We have concerns about the company's preferred estimates, which use trial data from Sub-Saharan Africa to approximate risk amongst women living in the UK. Epidemiology, healthcare delivery and access to services vary markedly between these contexts.

The most credible estimate of incidence in eligible cisgender women that we are aware of is from a study of SHS attendees between 2009-2013 (Aghaizu, 2018). Incidence amongst black African heterosexuals was estimated to be 0.19/100 person-years in 2013. The number of new HIV diagnoses amongst women first diagnosed in the UK was [redacted] in 2023 compared to [redacted] in 2015 (unpublished UKHSA analysis, earlier data is not available). We note that incidence amongst MSM in the same study was 1.46/100 person years. This illustrates that the incidence rate from eligible MSM cannot be used to infer that of cisgender women.

Aghaizu, Adamma, Jennifer Tosswill, Daniela De Angelis, Helen Ward, Gwenda Hughes, Gary Murphy, and Valerie Delpech. 'HIV Incidence among Sexual Health Clinic Attendees in England: First Estimates for Black African

Heterosexuals Using a Biomarker, 2009-2013'. Edited by Dimitrios Paraskevis. PLOS ONE 13, no. 6 (20 June 2018): e0197939. https://doi.org/10.1371/journal.pone.0197939.

Cambiano, Valentina, Alec Miners, Fiona C Lampe, Sheena McCormack, O Noel Gill, Graham Hart, Kevin A Fenton, et al. 'The Effect of Combination Prevention Strategies on HIV Incidence among Gay and Bisexual Men Who Have Sex with Men in the UK: A Model-Based Analysis'. The Lancet HIV 10, no. 11 (November 2023): e713–22. https://doi.org/10.1016/S2352-3018(23)00204-7.

Donnell, Deborah, Kidist Zewdie, Natasha Ratna, Veronica Miller, John Michael Saunders, O Noel Gill, Valerie Delpech, and Hamish Mohammed. 'Association between Rectal Gonorrhoea and HIV Incidence in Men Who Have Sex with Men: A Meta-Analysis'. Sexually Transmitted Infections 98, no. 7 (November 2022): 492–96. https://doi.org/10.1136/sextrans-2021-055254.

Sullivan, Ann K, John Saunders, Monica Desai, Andrea Cartier, Holly D Mitchell, Sajjida Jaffer, Dana Ogaz, et al. 'HIV Pre-Exposure Prophylaxis and Its Implementation in the PrEP Impact Trial in England: A Pragmatic Health Technology Assessment'. The Lancet HIV 10, no. 12 (December 2023): e790–806. https://doi.org/10.1016/S2352-3018(23)00256-4.

UK Health Security Agency. 'HIV Action Plan Monitoring and Evaluation Framework 2023 Report'. UK Health Security Agency, 2023. https://www.gov.uk/government/publications/hiv-monitoring-and-evaluation-framework/hiv-action-plan-monitoring-and-evaluation-framework-2023-report.

Starting age of people in the model:

There is limited data available on the age at which people initiate PrEP. 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). However, we note that the 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).

In addition, there is evidence that individuals are most likely to have multiple sexual partners between the ages of 16 and 24. Data from the National Survey of Sexual Attitudes and Lifestyles (NATSAL) 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). We caveat that this evidence relates to heterosexual sex.

Mercer, Catherine H, Clare Tanton, Philip Prah, Bob Erens, Pam Sonnenberg, Soazig Clifton, Wendy Macdowall, et al. 'Changes in Sexual

Attitudes and Lifestyles in Britain through the Life Course and over Time: Findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal)'. The Lancet 382, no. 9907 (November 2013): 1781–94. https://doi.org/10.1016/S0140-6736(13)62035-8.

UK Health Security Agency. 'Official Statistics for HIV Testing, PrEP, New HIV Diagnoses and Care Outcomes for People Accessing HIV Services: 2024 Report'. UK Health Security Agency, 2024. https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2024-report.

Name	[redacted]
Organisation	N/A
Conflict	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

I think this has been missed:

https://www.who.int/publications/i/item/9789240054097

WHO on cabotegravir, while you quote it in reference 83, you don't address why you go against this advice.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. You have decided to redefine a negative (those people unable or unwilling to take oral PrEP) and assumed that as that negative cannot actually be defined, you have concluded there probably isn't a positive and so do not want to go against the UK licence of the medication.

The HIV clinic in Dean street clinic, London, reviewed individuals who stopped their PrEP and concluded 25% of new HIV diagnoses were in MSM's who took a 'PrEP' holiday. The question could be, could these of been prevented if on injectables? I know you can not answer this, but this is a reason to give out PrEP injectables as part of a national trial, to see if this figure of PrEP holiday HIV diagnoses, reduces or not.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Comment below are in answering the section: 'Why the committee made these recommendations'

Absolutely not. You have just restated its marketing authorisation, and ignored the WHO, and other experience from sexual health practitioners/clinics and other organisations.

In your first paragraph you state the need, in people who are unable to take oral PrEP and there are no other options available - cabotegravir closes this gap, you have clearly stated that need. You have also stated the need in section B.1.3.6, you have stated the need very clearly, but have ignored all in the first paragraph.

2nd Paragraph, there is no trial comparing cabotegravir directly compared with no PrEP - of course not, that approach would be unethical, there is already a gold standard, this is oral PrEP, so the only ethical trial to do is cabotegravir against oral PrEP, this has been done and cabotegravir is effective, as stated by yourselves. The NICE committee should know this and stating no evidence in the 2nd paragraph shows very poor judgement.

3rd: There are no difficulties in determining who would need cabotegravir, this would largely be a self sorting group, people who are taking PrEP incorrectly, not getting timely refills, people unable to take PrEP (TAF form) or Descovy form.

If you want to highlight a risk (which in the recommendations you don't), highlight the rate of A6 subtype, as could be an indicator for injectable failure if used as PrEP but this could also be a definable population, this is your get out, but you have ignored it.

4th paragraph, No evidence is fully generalisable to the whole population, where will always be groups where advice doesn't fit. However there are groups that have been defined that are at risk of HIV. Limited access to cabotegravir could be given under circumstances as set out above and decided by the clinical team on the ground if they will give this medication or not, on a case by case bases. At first this could be run as a trial, to help gather data which will assess future direction and use of cabotegravir as PrEP.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes, I think the recommendations do not consider the risk some groups have in contracting HIV. MSM's in London and Black women outside of the capital have higher risk profiles and I think these two groups are being side lined because of the lack of generalisability. I would advise NICE to reconsider as while the uptake of cabotegravir will be low and mostly declined by most clinical teams as oral PrEP will be more suitable; there will be cases where injectables would clearly of prevented HIV transmission and these recommendations look to discriminate these two groups from the outset.

Name	[redacted]
Organisation	N/A

Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No, for reasons described in my comment.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, for reasons described in my comment.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Yes, for reasons described in my comment.

Comment on section 3.3, positioning of cabotegravir

I vehemently disagree with the committee's views that the group of people who do not take oral PrEP exactly as prescribed is "a difficult subpopulation to define in clinical practice". Frontline sexual health workers and doctors can usually quite easily identify this subpopulation within their list of patients based on consultation and discussions and providing this additional option for PrEP would be incredibly beneficial to ensuring these patients' risk for HIV is reduced. I also disagree with the committee's framing that this subpopulation must be based on "defined characteristics". Many other medications are offered in different formulations based on the individual patient's life circumstances rather than generic population characteristics like race, sexual orientation, etc. There is no reason why the same cannot apply for PrEP formulations. In fact, refusing to do so can be seen as punitive towards people whose life circumstances do not allow themselves to easily adhere to daily oral PrEP. Furthermore, this cohort of individuals are likely those at increased risk of HIV acquisition (people who use drugs, people who engage in sex work, people who are homeless). Not only could refusing to offer long-acting injectable PrEP be considered discriminatory towards these groups, but it also would be cost-ineffective, as these cohort tend to have higher overall costs associated with their care (including HIV care) and offering PrEP in a form suitable to them would realise savings in the long-term by preventing future HIV care costs.

Name	[redacted]

Organisation	N/A
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

The committee noted there was no evidence comparing CAB-LA to no PrEP. However, this would be challenging from an ethical perspective. Furthermore, data obtained from clinical trials with a 'No PrEP' arm would be limited, as trials would likely need to be stopped early due to superior efficacy in the intervention arm (as with early PrEP studies). A large sexual health clinic in London found that only 1-2% of their 25,000 PrEP users required consultant review due to intolerance or contraindications to PrEP. These represent a small and clinically heterogeneous population of individuals for whom it would be extremely difficult to design a clinical trial to confirm that CAB-LA PrEP would be efficacious.

Identifying women who are not engaged in PrEP care but would opt for non-oral PrEP is challenging. A modelling study has estimated the efficacy of CAB-LA versus no PrEP to be 93-95% (Donnell D et al. Counterfactual estimation of efficacy against placebo for novel PrEP agents using external trial data: example of injectable cabotegravir and oral PrEP in women. J Int AIDS Soc. 2023 Jun;26(6):e26118.).

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is inevitable that the costs of keeping some people free of HIV will be greater than others.

The technology appraisal documents indicate that patients using CAB-LA PrEP are likely to require up to 60 minutes of Clinician time (testing, administration, documentation). Medium and large sexual health services could streamline CAB-LA PrEP appointment times to less than an hour by leveraging existing pathways for injectable HIV treatment (which requires two injections versus one for PrEP). With efficient administration and observation protocols, patients could experience shorter appointment durations. I work in a large sexual health clinic in London which manages continuation injections of CAB-LA (via compassionate use) in 20 minute nurse-led appointments with post injection waiting time in the waiting room, as standard of care with other injectable medicines given within GUM services.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Recommendations state it would be difficulty to identify individuals who would benefit from CAB-LA

Cabotegravir is increasingly prescribed within NHS England's commissioned HIV services in combination with rilpivirine, following NICE approval for

injectable antiretroviral therapy (ART) in 2022. However, there has not been a significant increase in requests from oral ART users to switch to injectables; instead, the number of patients on injectable ART has risen gradually over time. Clinic capacity may limit the provision of injectable therapy, which will need to be managed locally. Therefore, a sudden surge in oral PrEP users transitioning to injectable CAB is unlikely.

British HIV Association guidance helped guide clinicians on individuals who would be suitable for injectable ART. BASHH PrEP guidelines (currently out for consultation) state: 'We recommend that long-acting injectable cabotegravir is strongly supported as an alternative to a daily PrEP pill (1A).' Data from our national PrEP MDT, a virtual review service which advises on individuals with complex needs, shows that CAB-LA was only recommended in 10.9% of all cases. We would urge that Cabotegravir is recommended for everyone who needs it. As experts, the sexual health MDT are best placed to determine who would benefit from which HIV prevention tool based on risk of acquisition, medical history, lifestyle and social factors.

Data from our large urban sexual health service found that 24% of individuals with newly diagnosed HIV had evidence of PrEP exposure with adherence challenges as the likely reason for PrEP failure. PrEP review appointments allow sexual health clinicians to identify PrEP adherence issues and provide relevant support. Therefore, routine PrEP follow-up care provides opportunities to identify individuals who may benefit from CAB-LA. Utilisation of post-exposure prophylaxis (PEP) in people with suboptimal PrEP adherence may further identify suitable individuals. Sexual health clinicians have a wealth of experience in identifying adherence issues with PrEP and ART and are well positioned to identify people who would benefit from CAB. Previous attendance history can be a reliable indicator of the likelihood of attending 2 monthly injection appointments.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

UKHSA 2023 data found that 28% of new HIV diagnoses first made in England were among women exposed through sex with men. GBMSM (gay, bisexual and other men who have sex with men) made up a similar proportion of new diagnoses (29%). Despite this, only 40.9% of heterosexual and bisexual women with a PrEP need, initiated or continued PrEP. This number was lower in non-white heterosexual and bisexual women. In comparison, 75.4% of GBMSM (gay, bisexual and other men who have sex with men) with a PrEP need initiated or continued PrEP. Clearly, further work is needed to engage women in PrEP services. Identifying women who are not engaged in PrEP care but would opt for non-oral PrEP is therefore challenging.

Descovy PrEP (emtricitabine/tenofovir alafenamide, F/TAF), an alternative to tenofovir disoproxil-based PrEP (F/TDF), was commissioned in May 2023 for those with kidney or bone related issues. However, Descovy is not licensed in cisgender women, creating inequity for women with contraindications to F/TDF PrEP. Therefore, a second PrEP option is required in this population.

Comments on draft guidance

HIV data from UKHSA in 2023 indicates that health inequalities are widening and achieving the goal of zero new HIV transmissions by 2030 is in jeopardy. To meet the objectives outlined in the Government's HIV Action Plan, it is essential to expand the range of available HIV prevention tools.

As a healthcare professional, I acknowledge that oral Tenofovir based PrEP remains a reliable and cost-effective option for preventing HIV acquisition. Despite this, a small proportion of patients struggle to take daily tablets due to adherence issues or privacy concerns. Some are unable to tolerate oral PrEP due to side effects, or may have medical contraindications to standard PrEP options. This represents a clear unmet need.

NICE and ViiV should work in unison in order to determine a drug price which is cost-effective to the health system, through utilisation of an enhanced patient access scheme (PAS) discount. NICE and ViiV should also consider managed access arrangement (MAA) as one potential commissioning route for CAB-LA, in favour of an outright decision to not commission CAB-LA. It should be noted that this has disadvantages, as NHS services not attached to an acute Trust may struggle to provide the drug due to the reporting requirements of an MAA. This may further entrench existing geographical disparities which currently limit access to Descovy PrEP.

Name	[redacted]
Organisation	University Hospitals Bristol and Weston NHS Foundation Trust
Conflict	N/A

Comments on the DG:

Are the recommendations sound and a suitable basis for guidance to the NHS?

Here in Bristol, North Somerset and South Gloucestershire, our UNITY Sexual Health service collaboration is hosted by UHBW.

Our concerns with the draft negative recommendations are as follows;

We are aware that whilst many of our clients are able to take oral PrEP options, there are three subsets for whom having the approved option of taking an injectable HIV PrEP such as Cabotegravir (Apretude®) would be more acceptable and clinically appropriate.

(a) those not eligible for Descovy® as medical diagnoses not covered by the Descovy® criteria, but also not able to take Truvada® due to renal/ bone issues or potential interactions on advice of their specialist teams (especially interactions on methotrexate and other DMARDS)

(b) those not able to take Truvada® due to renal / bone issues but also not able or willing to take daily PreP - as Descovy® has to be taken Daily

(c) those not able to take tablets at all (either physically unable or just cannot reliably remember) but feel would be able to commit to injections

We suggest that NICE consider approving Cabotegravir as an option for when an oral option is either unsuitable or contraindicated. We believe that moving to that position would be entirely appropriate and evidence-based.

Name	[redacted]
Organisation	HIV i-Base
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Thank you for the chance to comment on the draft guidance and recommendations related to access to injectable cabotegravir as HIV PrEP.

It is difficult to understand why NICE decided to base cost-effectiveness on the assumption that everyone who theoretically could use CAB-LA PrEP based on the MHRA indication is likely to want to use this treatment.

For example, a large percentage of people who would otherwise have high risk factors for HIV transmission are already covered but using oral PrEP.

It is timely to note that the BASHH/BHIVA updated PrEP guidelines released earlier this month make oral PrEP even easier to use. This includes the greater flexibility that everyone can now start PrEP with a double dose to achieve protective drug levels within two hours. The guidelines reduce the adherence threshold for high levels of protection to broadly only needing four doses a week rather than 6-7 previously recommended for cisgender women and trans and non-binary people. The guidelines also open the option of event-based PrEP irrespective of sex or gender, making oral PrEP a relatively easier and more accessible choice. These factors in themselves are likely to lessent the interest in injectable PrEP for many people.

Instead, injectable PrEP is important for relatively smaller subgroups of individuals, as outlined in detail in the submissions to the initial NICE consultation by community advocates, including from the UK-CAB.

I still hope that the submission of new cost-effectiveness data are sufficient to allow CAB-LA to be approved with a PrEP indication. If for any reason access to CAB-LA is blocked because of the higher cost-effectiveness barrier, then the decision by NICE will not have been one of facilitating more equitable access, but one of denying access to people who are currently at disproportionally higher risk of HIV for social and economic reasons detailed in the original community submissions.

PrEP is prescribed by doctors who are already experienced in understanding the needs of different people at high risk of HIV. Rather than defaulting to the lack of data purely collected in the proposed sub-groups of people who would particularly benefit from injectable PrEP - many of who were actually also included in phase 3 CAB-LA studies - NICE should actively suggest guidance for how to facilitate access rather than blocking it.

As scientific advances enable new formulations and choices for PrEP, these have a mosaic impact on expanding the population who could now benefit. Injectable PrEP expands this population group to include people who would never find oral PrEP acceptable. NICE decisions on approval and access were be more helpful if this was actively recognised and acknowledge, rather than looking backwards to assume the market depends on including the existing population of people are are happily using oral PrEP and who have no intention to change.

Thank you for consideration of these comments.

Name	[redacted]
Organisation	Chelsea and Westminster Hospital NHS Foundation Trust
Conflict	N/A
Comments on the DG:	

Comment on section 1, recommendations

Dear NICE,

We would like to respond to the recent NICE decision regarding cabotegravir.

I'm writing on behalf of the PrEP clinical group from Chelsea and Westminster NHS Trust.

Firstly, we are concerned about the delay in accessing long acting cabotegravir for those who urgently require PrEP options that do not involve tenofovir disoproxil, emtricitabine or tenofovir alafenamide, emtricitabine. We currently have patients who are in urgent need of alternative PrEP formulations and are concerned about delays to their HIV prevention care. Delays in accessing cabotegravir will impact those with co-morbidities and health inequities. The most recent UKHSA reported a 15% rise in new HIV transmission in England in 2023, a clear warning sign that we are not on course to meet the government's target to eliminate new infection in England by 2030. As such there is an urgent need to expand the breadth and reach of effective HIV prevention tools. Intramuscular cabotegravir has demonstrated superiority to oral tenofovir disoproxil, emtricitabine PrEP in two large RCTs with the majority seroconversions in the oral tenofovir disoproxil, emtricitabine arm likely to be secondary to non-adherence to oral PrEP. This offers clear evidence for the advantage of long-acting cabotegravir in those with adherence difficulties. Data from 56 Dean Street, a large sexual health service within Chelsea and Westminster NHS Trust, 24% of individuals with newly diagnosed HIV had evidence of PrEP exposure with adherence challenges the likely reason for PrEP failure. We risk delaying access to a medication which may provide superior efficacy for HIV prevention to these individuals and adding to other health inequalities that they already experience.

Secondly, we understand one of the outcomes of the committee decision was the lack of data of cabotegravir in groups struggling to take tenofovir disoproxil, emtricitabine or tenofovir alafenamide, emtricitabine. Whilst limited, there are observation data to demonstrate a need in those who are unable to take, or struggle to take, tenofovir disoproxil, emtricitabine in real-world settings in the UK. 56 Dean Street found 1-2% of the population required consultant-review due to patient reported issues and or drug toxicity with tenofovir disoproxil, emtricitabine. These represent a small and clinically heterogeneous population of individuals for whom it would be extremely difficult to design a clinical trial to confirm that cabotegravir prep would be efficacious. Our experience suggests that these individuals are motivated to attend for regular appointments for injection administration and there is no biological reason why we would expect cabotegravir prep to be less efficacious, given its superiority over tenofovir disoproxil, emtricitabine in PrEP trials.

Comment on section 3.15, cabotegravir administration costs

Thirdly, we have a practical point regarding the time for appointments that have been suggested. With PrEP users requiring cabotegravir via

compassionate use, we offer 30 to 40 minute doctor consultation appointment at first appointment and again on day of first injection. Subsequent appointments are managed in 20 minute nurse-led appointments with post injection waiting time in the waiting room (as standard of care with other injectable medication given in our service).

EAG response to stakeholder feedback

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

Produced by	*Warwick Evidence*
Date completed	*25/10/2024*

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR165475.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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1 Background

After the first committee meeting the National Institute for Health and Care Excellence (NICE) circulated draft guidance for consultation with stakeholders. The recommendation was:

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.

The committee concluded that further analysis using the whole population eligible for PrEP is necessary for the committee to make recommendations.

The committee preferred the cost-effectiveness model to include:

- both TDF/FTC and no PrEP as comparators
- adherence to TDF/FTC to be lower for cis women compared with MSM and trans women
- a baseline HIV acquisition value of 3.9 per 100 person-years
- a HIV risk period of 10 years
- the starting age of the model population to be 33 years
- cabotegravir administration costs to be based on 1 hour of clinic time
- cabotegravir administration every 2 months
- a disutility of -0.11 associated with living with HIV.

The company submitted an amended base case with the following changes

1. Baseline risk of HIV acquisition updated to 3.9 per 100 person-years (PY)

2. Discontinuation rate implementation corrected to apply rate for 6 months instead of 5 months

3. Error in the data selection from one study used in the indirect treatment comparison (ITC) corrected and uncertainty in adherence measurement incorporated

4. Starting age and population distribution updated in line with new data from the UKHSA.

5. Error in the frequency of renal function tests applied to cabotegravir and TDF/FTC in the cost-effectiveness analysis identified and corrected in line with the BHIVA/BASHH guidelines.

The EAG has critiqued the amended base case and considered other consultation responses from stakeholders to the draft guidance.

2 Issues arising from company and committee concerns

2.1 Whole population eligible for cabotegravir

The company accepts the use of the whole population eligible for cabotegravir, including those who take oral PrEP exactly as prescribed, stating that their original base-case reflects the whole population. As discussed further in Section 3.3, the company agreed to the baseline HIV incidence of 3.9/100 person years preferred by the committee. However, this estimate was taken from the population of men who have sex with men with a recent rectal bacterial STI and is not appropriate for the whole population eligible for cabotegravir. The EAG notes that the recent data from the UK[1] report the baseline HIV incidence to be 0.95/100 person years for the whole population. This rate was also recommended in the UKHSA response to the NICE draft guidance. The EAG has modelled this rate in the EAG updated base case.

2.2 Adherence to TDF/FTC to be lower for cis women compared with MSM and trans women

The EAG retains its base case assumptions on equivalent adherence between cisgender women and men who have sex with men and transgender women populations.

2.3 Baseline HIV acquisition value.

The EAG agrees with the committee's preference for a broader population in this appraisal and re-states that the population modelled by the company in its original submission reflects the committee's preferred population. The re-defined population for the appraisal has implications for the baseline HIV incidence rate used in economic model. Our previous estimate, which reflects the narrower population previously defined, was from a study conducted in 2014 which reported HIV incidence in men who have sex with men with recent rectal bacterial STI. HIV incidence in the UK population who could take cabotegravir as prescribed, including those currently taking oral PrEP (inclusive of non-adherent PrEP users) is estimated to be 0.95 per 100 person years from a recent study with a sample size of 1,506,410 users across 157 of 227 Sexual Health Services in England between October 2017 and July 2020.[1]

Given the re-defined population, the EAG notes that the presence of a recent rectal bacterial STI is not a pre-requisite for being on PrEP. Also, such markers can be misleading, as the incidence of STIs has risen between 2010 to 2020, while HIV incidence fell within that period.[2]

2.4 HIV risk period

We retain our previous base case assumption of a 10-year risk period.

2.5 Starting age of the model population

We retain our previous base case assumption of model starting age of 33 years.

2.6 Clinic time for cabotegravir administration costs

The EAG wishes to highlight a factual inaccuracy in the company's description of the EAG assumptions around cabotegravir administration time. The company stated *"The EAG's preferred assumption implies that each subsequent injection visit will take 90 minutes as it applies 20 minutes of Band 5 nurse time for observation, 40 minutes of clinical activity and 30 minutes of medical consultant time"*. This is factually inaccurate as our 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 (calculated as the weighted average of a Band 6 Nurse, Pharmacist and Sexual Health consultant). We have updated the costs

applied for a sexual health consultant time, as the previous estimate used reflected costs associated with a unit of clinical activity rather than wages.

Following the consultation process, the EAG has updated its base case to include an hour of clinical activity for the first two injection visits, i.e., 20 mins of observation by a Band 5 Nurse and 40 mins of clinical activity/drug administration (calculated as the weighted average of 40 minutes of a Band 6 Nurse, Band 6 Pharmacist and NHS consultant wages). Subsequent injection visits are assumed to incur an administration time of 30 mins and assumed to be administered by a Band 6 Nurse.

In our previous base case, administration was assumed to incur 13 minutes of a medical consultant's time rather than 30 mins claimed by the company. Our current base case includes 13 minutes of a medical consultant's time for the first two injection visits only.

2.7 Cabotegravir administration every 2 months

We retain our previous base case assumptions.

2.8 Disutility of -0.11 associated with living with HIV

We retain our previous base case assumptions.

3 Additional issues in revised company base case

3.1 Discontinuation rate implementation corrected

The EAG disagrees with the updated discontinuation rate. The company's claim that discontinuation rates were applied for five 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. When discontinuation rates were applied for 6 months, the ICER rises above the £30,000 per QALY threshold.

It should be noted that the cycle begins from Month 1 and not 0. Hence, the cohort would have spent six months in the various health states at the end of the 6th cycle.

3.2 Error in the data selection from one study used in the indirect treatment comparison (ITC) corrected and uncertainty in adherence measurement incorporated

The data extraction error relates to the Partners PrEP study,[3] where efficacy data were mistakenly extracted for the TDF arm instead of the TDF/FTC arm. The company's correction of this error has had minimal impact on the effectiveness estimates. Although the EAG has not updated its own ITC, the EAG has incorporated the company updated estimates in the base case. The change has minimal impact on the cost-effectiveness.

The EAG welcomes the company's revision of its base-case to account for uncertainty in the adherence measures used in the revised economic model. Since adherence is not directly observed in the trials, its measurement is uncertain. Failing to account for this measurement error could lead to biased estimates of the relationship between efficacy and adherence, potentially resulting from regression attenuation bias or regression to the mean.

3.3 Error in the frequency of renal function tests applied to cabotegravir and TDF/FTC in the cost-effectiveness analysis identified and corrected in line with the BHIVA/BASHH guidelines

The EAG cannot verify the company's claim about requirements for renal function tests in PrEP users on TDF/FTC and cabotegravir. However, we have included the updated frequency of renal function tests in our base case.

4 Company cost effectiveness results

The company cost-effectiveness results is presented in the Tables and Figures below using cabotegravir list price.

Table 1: Company deterministic base-case cost-effectiveness results for cabotegravir versus TDF/FTC (cabotegravir list price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2: Company deterministic base-case cost-effectiveness results for cabotegravir versus no PrEP (cabotegravir list price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: Company probabilistic base-case cost-effectiveness results for cabotegravir versus TDF/FTC (cabotegravir list price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1 Cost-effectiveness Plane

Figure 2 Cost-effectiveness acceptability curve

5 EAG exploratory cost effectiveness results

The EAG assumptions are detailed below.

EAG 01: Baseline risk of HIV acquisition

Due to the uncertainty around the estimate used for the baseline risk of HIV acquisition, the EAG prefers a baseline risk of 0.95 per 100 person-years for men who have sex with men and transgender women and 0.74 per 100 person years for cisgender women. This incidence rate reflects the HIV incidence PrEP eligible individuals.

EAG 02: Patients who stop cabotegravir PrEP do not transition to receive oral PrEP

The company argues that the population considered for cabotegravir PrEP are those for whom oral PrEP is inappropriate while simultaneously assuming that [redacted] of patients on stop cabotegravir PrEP subsequently go on to receive oral PrEP. A similar assumption is not made in the oral TDF/FTC group which biases the ICER in favour of cabotegravir. The EAG prefers no transitioning from cabotegravir to oral PrEP.

EAG 03: **Adherence to TDF/FTC**

Due to the lack of evidence showing gender-based differences in adherence to oral PrEP in the UK, and the unreliability of adherence data from the HPTN 084 study which was conducted in participants from sub-Saharan Africa, the EAG prefers to set adherence for cisgender women equal to transgender women and men who have sex with men.

EAG 04: Persistence to cabotegravir

Due to the lack of evidence on the company's base case assumption of improved persistence of cabotegravir compared to oral PrEP, the EAG considers no relative improvement in persistence to cabotegravir compared to oral PrEP.

EAG 05: Per cycle application of ISR costs and disutility

Costs of treating ISR was also applied per cycle rather than as a one-off cost. A disutility value of –0.015 was assumed for ISR and applied per cycle.

EAG 06: Duration of risk period

Duration of on-risk period changed from 5 years to 10 years to account for uncertainties associated with a shorter risk period.

EAG 07: Cabotegravir administration costs

Administration costs for cabotegravir costs changed from company base case to an hour of activity in the clinic (i.e. 20 mins band 5 nurse for observation, 40 mins clinical activity representing the weighted average a pharmacist, consultant, and clinical nurse specialist wage for the first two injection visits and 30 mins of clinical activity for subsequent visits.

EAG 08: Cabotegravir dosing schedule

Cabotegravir was assumed to be administered every 8 weeks rather than 2 months in the company base case. EAG preferred frequency of visit was applied to cabotegravir administration costs and cabotegravir HIV antigen tests cost.

EAG 09: Cabotegravir acquisition costs

Drug acquisition and administration costs for cabotegravir increased by 5% to account for potential increases in lifetime costs of cabotegravir administration during to changing risk patterns over the lifetime of the cohort.

EAG 10: Starting age of model

The starting age of the model cohort was increased from 26 years to 33 years to match the median age of PrEP users in the UK

EAG 11: Disutility for HIV

Disutility for HIV changed from –0.11 to -0.05

EAG 12: Improved persistence, i.e. continuation rate, applied for 6 months rather than 7 months in the company base case.

The impact of the EAG preferred model assumptions can be seen in Table 4.

Table 4: Impact of individual EAG preferred model assumptions on ICER (Cabotegravir vs TDF/FTC)

Preferred assumption	Incremental cost	Incremental QALYs	ICER
Company base case	[redacted]	[redacted]	[redacted]
EAG01	[redacted]	[redacted]	[redacted]
EAG02:	[redacted]	[redacted]	[redacted]
EAG03:	[redacted]	[redacted]	[redacted]
EAG04:	[redacted]	[redacted]	[redacted]
EAG05:	[redacted]	[redacted]	[redacted]
EAG06:	[redacted]	[redacted]	[redacted]
EAG07:	[redacted]	[redacted]	[redacted]
EAG08:	[redacted]	[redacted]	[redacted]
EAG09:	[redacted]	[redacted]	[redacted]
EAG 10:	[redacted]	[redacted]	[redacted]
EAG 11:	[redacted]	[redacted]	[redacted]
EAG 12:	[redacted]	[redacted]	[redacted]

5.1.1 EAG deterministic base case results

The cumulative effect of the EAG changes on the company deterministic base case is shown in the Tables below. Cabotegravir had incremental costs of [redacted] and QALYs of [redacted]. The ICER for the base case is [redacted].

Table 5: EAG deterministic base-case cost-effectiveness results for cabotegravir versus TDF/FTC (cabotegravir list price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: EAG deterministic base-case cost-effectiveness results for cabotegravir versus no PrEP (cabotegravir list price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
No PrEP	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: EAG probabilistic base-case cost-effectiveness results for cabotegravir versus TDF/FTC (cabotegravir list price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)
TDF/FTC	[redacted]	[redacted]	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3 Cost-effectiveness plane (cabotegravir vs TDF/FTC) using EAG base case assumptions

Figure 4 Cost effectiveness acceptability curve (cabotegravir vs TDF/FTC) using EAG base case assumptions

6 References

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3. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012;367(5):399-410. DOI: 10.1056/NEJMoa1108524.

ID6255: Cabotegravir for preventing HIV-1 in adults and young people. External Assessment Group (EAG) Report: Additional analyses

Produced by	*Warwick Evidence*
Authors	Henry Nwankwo, Assistant Professor, Warwick Evidence, University of Warwick Jill Colquitt, Senior Reviewer, Effective Evidence LLP Felix Achana, Honorary Senior Research Fellow, Warwick Evidence, University of Warwick Naila Dracup, Information Specialist, Warwick Evidence, University of Warwick Pranshu Mundada, Research Associate, Warwick Evidence, University of Warwick Priyanka Chaudhuri, Research Associate, Warwick Evidence, University of Warwick Angela Mwape, Research Fellow, Warwick Evidence, University of Warwick. Emma Loveman, Senior Reviewer, Effective Evidence LLP Lena Al-Khudairy, Associate Professor, Warwick Evidence, University of Warwick
Correspondence to	*Henry Nwankwo* *henry.nwankwo@warwick.ac.uk*
Date completed	*11.11.2024*

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR136178.

Declared competing interests of the authors

None.

Acknowledgements

We thank Professor Julie Fox (Guys and St Thomas' NHS Trust/ Kings College London) for supporting and answering clinical queries in relation to this appraisal.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Contributions of authors

Henry Nwankwo and Pranshu Mundada (Health Economists) critiqued the cost-effectiveness evidence, undertook EAG's modelling and produced this confidential appendix. Lena Al-Khudairy (Associate Professor), Jill Colquitt (Senior Reviewer) and Felix Achana (Honorary Senior Research Fellow) critiqued clinical effectiveness evidence. Angela Mwape (Research Fellow), Priyanka Chaudhuri (Research Associate) and Emma Loveman (Senior Reviewer) supported the critique of the clinical effectiveness evidence. Naila Dracup (Information Specialist) critiqued the company's searches and conducted additional EAG searches. Lena Al-Khudairy coordinated the project. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

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Additional analyses

In this document, we have undertaken further analyses as requested by NICE, which uses the PAS price for cabotegravir, rather than the list price.

This document is structured as follows:

1) A re-run of all analyses contained in the EAG document 'ID6255 cabotegravir DG response EAG 25102024' using the cabotegravir PAS price. These include:

- Company deterministic results for cabotegravir versus TDF/FTC
- Company deterministic results for cabotegravir versus no PrEP
- Company probabilistic results for cabotegravir versus TDF/FTC
- EAG exploratory results on the company's deterministic base-case results
    - EAG 01: Baseline risk of HIV acquisition
    - EAG 02: Patients who stop cabotegravir PrEP do not transition to receive oral PrEP
    - EAG 03: Adherence to TDF/FTC
    - EAG 04: Persistence to cabotegravir
    - EAG 05: Per cycle application of ISR costs and disutility
    - EAG 06: Duration of risk period
    - EAG 07: Cabotegravir administration costs
    - EAG 08: Cabotegravir dosing schedule
    - EAG 09: Cabotegravir acquisition costs
    - EAG 10: Starting age of model
    - EAG11: Disutility for HIV
- EAG deterministic results for cabotegravir versus TDF/FTC
- EAG deterministic results for cabotegravir versus PrEP
- EAG probabilistic sensitivity analysis results for cabotegravir versus TDF/FTC

2) Using the EAG preferred assumptions, a re-run of the following scenario analyses undertaken/provided by the company:

- Scenario analysis for cabotegravir versus TDF/FTC in the population where 100% of individuals have detectable TFV plasma levels (cabotegravir PAS price vs TDF/FTC list price) – see Table 4 in company's DG response for details
- Scenario analysis for cabotegravir versus TDF/FTC with the two varied percentages of people transitioning from cabotegravir to TDF/FTC (cabotegravir PAS price vs TDF/FTC list price) – see Table 7 in company's DG response for details
- Scenario analysis for cabotegravir versus TDF/FTC, 10% improvement in persistence with cabotegravir (cabotegravir PAS price vs TDF/FTC list price) – see Table 9 in company's DG response for details
- Scenario analysis for cabotegravir versus no PrEP, 10% improvement in persistence with cabotegravir (cabotegravir PAS price) – see Table 10 in company's DG response for details

3) Using the committee's preferred assumptions from the first meeting:

    - baseline HIV acquisition value of 3.9 per 100 PY
    - HIV risk period of 10 years
    - adherence to TDF/FTC to be lower for cis women compared with men who have sex with men and trans women
    - starting age of the model population to be 33 years
    - cabotegravir administration costs to be based on 1 hour of clinic time
    - cabotegravir administration every 2 months
    - a disutility of -0.11 associated with living with HIV
- Scenario analysis for cabotegravir versus no PrEP using committee's preferred assumptions from the first committee meeting listed above (cabotegravir PAS price)

In all analyses we report, total costs, total QALYs, incremental costs and incremental QALYs and ICER and incremental NHB at both £20,000/QALY and £30,000/QALY.

1.1 Company's cost effectiveness results- with using PAS price

1.1.1 Company deterministic base-case results

Table 1: Company deterministic base-case cost-effectiveness results for cabotegravir versus FTC/TDF

Technologies	Total costs (£)	Total QALY	Incremental costs (£)	Incremental QALY	ICER (£/QALY)	INHB	
						WTP £20,000	WTP £30,000
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FTC/TDF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; INMB, incremental net health benefit; QALY, quality adjusted life years; WTP, willingness-to-pay							

Table 2: Company deterministic base-case cost-effectiveness results for cabotegravir versus no PrEP

Technologies	Total costs (£)	Total QALY	Incremental costs (£)	Incremental QALY	ICER (£/QALY)	INHB	
						WTP £20,000	WTP £30,000
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FTC/TDF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; INMB, incremental net health benefit; QALY, quality adjusted life years; WTP, willingness-to-pay							

1.1.2 Probabilistic sensitivity analysis results

Table 3: Company PSA results for cabotegravir versus FTC/TDF

Technologies	Total costs (£)	Total QALY	Incremental costs (£)	Incremental QALY	ICER (£/QALY)	INHB	
						WTP £20,000	WTP £30,000
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FTC/TDF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALY, quality adjusted life years; WTP, willingness-to-pay							

Figure 1: Company incremental cost-effectiveness scatterplot for the comparison between cabotegravir compared to FTC/TDF

Figure 2: Company cost-effectiveness acceptability curve for the comparison between cabotegravir versus FTC/TDF

1.1.3 Scenario analysis results

Table 4: EAG exploratory results on the company's deterministic results

	Cabotegravir		FTC/TDC		Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)	INHB (WTP, £20,000)	INHB (WTP, £30,000)
Scenario	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs					

Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	Baseline risk of HIV acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Patients who stop cabotegravir PrEP do not transition to receive oral PrEP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Adherence to TDF/FTC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	Persistence to cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	Per cycle application of ISR costs and disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	Duration of risk period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Cabotegravir administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	Cabotegravir dosing schedule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	Cabotegravir acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	Starting age of model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11	Disutility for HIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALY, quality adjusted life years; WTP, willingness-to-pay										

1.1.4 EAG deterministic EAG deterministic results for cabotegravir versus FTC/TDF

Table 5: EAG deterministic cost-effectiveness results for cabotegravir versus FTC/TDF

Technologies	Total costs (£)	Total QALY	Incremental costs (£)	Incremental QALY	ICER (£/QALY)	INMB	
						WTP £20,000	WTP £30,000
FTC/TDF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALY, quality adjusted life years; WTP, willingness-to-pay

1.1.5 EAG deterministic results for cabotegravir versus no PrEP

Table 6: EAG deterministic cost-effectiveness results for cabotegravir versus no PrEP

Technologies	Total costs (£)	Total QALY	Incremental costs (£)	Incremental QALY	ICER (£/QALY)	INMB	
						WTP £20,000	WTP £30,000
No PrEP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALY, quality adjusted life years; WTP, willingness-to-pay

1.1.6 EAG probabilistic sensitivity analysis results for cabotegravir versus TDF/FTC

Table 7: EAG PSA cost-effectiveness results for cabotegravir versus FTC/TDF

Technologies	Total costs (£)	Total QALY	Incremental costs (£)	Incremental QALY	ICER (£/QALY)	INHB	
						WTP £20,000	WTP £30,000
FTC/TDF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; QALY, quality adjusted life years; WTP, willingness-to-pay							

Figure 3: EAG incremental cost-effectiveness scatterplot for the comparison between cabotegravir versus FTC/TDF

Figure 4: EAG cost-effectiveness acceptability curve for the comparison between cabotegravir versus FTC/TDF

1.1.7 Scenario analyses using the EAG preferred assumptions

- Scenario analysis for cabotegravir versus TDF/FTC in the population where 100% of individuals have detectable TFV plasma levels (cabotegravir PAS price vs TDF/FTC list price) – see Table 4 in company's DG response for details
- Scenario analysis for cabotegravir versus TDF/FTC with the two varied percentages of people transitioning from cabotegravir to TDF/FTC (cabotegravir PAS price vs TDF/FTC list price) – see Table 7 in company's DG response for details
- Scenario analysis for cabotegravir versus TDF/FTC, 10% improvement in persistence with cabotegravir (cabotegravir PAS price vs TDF/FTC list price) – see Table 9 in company's DG response for details
- Scenario analysis for cabotegravir versus no PrEP, 10% improvement in persistence with cabotegravir (cabotegravir PAS price) – see Table 10 in company's DG response for details

Table 8: Scenario analyses using the EAG preferred assumptions

Scenario		Cabotegravir		FTC/TDC		Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)	INHB (WTP, £20,000)	INHB (WTP, £30,000)
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs					
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	100% of individuals have detectable TFV plasma levels	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2a	25% of people transitioning from	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	cabotegravir to FTC/TDF									
2b	75% of people transitioning from cabotegravir to FTC/TDF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	10% improvement in persistence with cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	Cabotegravir versus no PrEP, 10% improvement in persistence with cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALY, quality adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; WTP, willingness-to-pay										

1.1.8 Committee preferred assumptions

In this analysis we use the committee's preferred assumptions. Where there are no changes, it is assumed that the company's assumptions apply.

- Baseline HIV acquisition value of 3.9 per 100 PY
- HIV risk period of 10 years
- Adherence to TDF/FTC to be lower for cis women compared with men who have sex with men and trans women per HPTN 083 and HPTN 084 trials

- Starting age of the model population to be 33 years
- Cabotegravir administration costs to be based on 1 hour of clinic time
- Cabotegravir administration every 2 months
- A disutility of -0.11 associated with living with HIV

Table 9: Deterministic results using the committee's preferred assumptions

Technologies	Total costs (£)	Total QALY	Incremental costs (£)	Incremental QALY	ICER (£/QALY)	IHMB	
						WTP £20,000	WTP £30,000
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FTC/TDF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; INHB, incremental net health monetary benefit; QALY, quality adjusted life years; WTP, willingness-to-pay							

Table 10: Scenario analysis results using the committee's preferred assumptions

		Cabotegravir		FTC/TDC		Incremental costs (£)	Incremental QALYs	ICER (cost per QALY)	INHB (WTP, £20,000)	INHB (WTP, £30,000)
Scenario		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs					
Committee's base-case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	Cabotegravir versus no PrEP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; INHB, incremental net health monetary benefit; QALY, quality adjusted life years; WTP, willingness-to-pay										

NICE National Institute for Health and Care Excellence

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

ViiV additional evidence submission – 11th April 2025

	As communicated on the 14th, March 2025, to enable the Committee to make a recommendation NICE is requesting from stakeholders' **additional evidence on the baseline risk of HIV acquisition** in people who would have cabotegravir or the comparators In addition, for completeness, NICE welcome **any further comments or points that stakeholders may wish to raise on other uncertainties** explored by the Committee
Organisation name	ViiV Healthcare.
Disclosure	Not applicable.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable.
Name of commentator person completing form:	ViiV Healthcare.

NICE National Institute for Health and Care Excellence

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

ViiV additional evidence submission – 11th April 2025

Executive Summary

ViiV Healthcare (ViiV) would like to thank the National Institute for Health and Care Excellence (NICE) and the Committee for their consideration of cabotegravir for the prevention of human immunodeficiency virus-1 (HIV-1) acquisition. ViiV express significant concern with the outcome of the second appraisal Committee meeting (ACM) and appreciate the opportunity to provide further evidence to enable the Committee to make a recommendation.

Baseline risk

Studies assessing the risk of HIV acquisition face significant limitations, especially within high-risk populations. This is due to the personal and multifactorial reasons that lead to an individual being exposed to HIV and the dynamic nature of HIV incidence, as well as the challenges in data collection that often fail to capture all markers of high risk. Despite these limitations, clinical experts at previous Committee meetings have highlighted that healthcare professionals (HCPs) experienced in prescribing PrEP are skilled at identifying high-risk individuals who would benefit from PrEP through their clinical interactions.

It is likely that incidence will be higher among people for whom oral pre-exposure prophylaxis (PrEP) is not appropriate, however it is not feasible to estimate HIV incidence in this population due to a lack of data granularity. Therefore, analyses using currently available datasets are likely to underestimate incidence among the high-risk individuals who could receive cabotegravir.

Considering the totality of relevant UK data and literature, incidence rates range from 3.9–17.4/100 person-years (PYs) in high-risk populations not receiving PrEP. Incidence rates of HIV are currently similar to the time periods of the studies identified, and there is a risk of increasing UK incidence through travel and migration, given that an additional 4·43–10·75 million new HIV acquisitions are estimated between 2025 and 2030 in low- and middle-income countries. Due to international funding cuts recently announced (1), a significant increase from the estimated 39.9 million people living with HIV today (2). Therefore, 3.9/100 PYs is a reasonable and conservative assumption to inform the cost-effective model base case.

To minimise the potential limitations associated with the ongoing and/or planned UK Health Security Agency (UKHSA) analyses, expert advisors have recommended the following:

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

ViiV additional evidence submission – 11th April 2025

Persistence

Multiple sources of real-world evidence (RWE) support that long-acting injectable interventions provide significant advantages regarding persistence over oral interventions, including PrEP. ViiV therefore maintain that cabotegravir is associated with a persistence improvement compared with oral PrEP.

Switching from cabotegravir to oral PrEP

Further RWE confirms that assuming 50% of people who discontinue cabotegravir switch to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is reasonable.

The duration of the high-risk period

ViiV maintain that a 5-year duration of high risk is most appropriate, and 10 years is excessive. This is supported by RWE of persistence and by feedback from clinical experts and stakeholders throughout the appraisal.

Further detail on the points in this section is provided in Table 1.

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

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Background and new evidence on unmet need for people at high risk of HIV acquisition

ViiV remain committed to working collaboratively with NICE to achieve access for people who could benefit from cabotegravir as HIV PrEP. Availability of broader prevention choices, such as long-acting PrEP, may help to address unmet needs in the current PrEP landscape (3), and to meet the UK Government's target of ending HIV transmissions (4).

According to the latest UKHSA data, new HIV diagnoses first made in England increased by 15% between 2022 and 2023, with the steepest rise observed among people exposed via sexual transmission between men and women (5). In addition, 27% of individuals who attended sexual health services (SHS) in England with an identified PrEP need did not initiate or continue oral PrEP (5), with regional disparities (6). As such, the UK is projected to miss the UK HIV Action Plan's target of zero new HIV transmissions by 2030 (4, 7). Indeed, recent trials suggest scepticism regarding efforts to achieve epidemic control by 2030 across the globe (8). Unmitigated reductions in funding may in fact reverse progress in the HIV response by 2030 (1, 9) alongside movement of people across borders, which may further increase the incidence of HIV within the UK (5). Continued and alternative efforts are therefore imperative to eradicate new HIV transmissions.

Oral PrEP is the only biomedical HIV prevention modality currently reimbursed in England (10). As discussed in Company Submission Document B (submitted 5th February 2024), significant unmet needs exist in the current PrEP landscape (11) relating to issues with oral PrEP adherence, persistence, and inadequate uptake. Drivers of PrEP unmet need include, but are not limited to, PrEP-related stigma (12), unacceptable dosing regimen, pill burden, and anxiety around missed doses (13-15). At a recent advisory board, a UK clinician noted [redacted] (16).

Cabotegravir is the first and only licensed long-acting injectable PrEP. Indeed, recently published evidence, including the latest cabotegravir implementation data, demonstrates that providing PrEP modalities that meet peoples' needs improve outcomes, including increased biomedical covered time and reduced HIV incidence (17-19). Across settings in East and Southern Africa, it has been shown that offering structured PrEP/post-exposure prophylaxis (PEP) choice, including cabotegravir, could reduce the incidence of HIV by one-third over 10 years (20). Another recently published modelling study in the Netherlands concluded that closing unmet PrEP needs by the rapid introduction of cabotegravir within the Dutch PrEP scheme could avert up to 21% of new acquisitions within 10 years, and accelerate achieving zero new HIV acquisitions (21).

The superior efficacy of cabotegravir versus oral PrEP has been demonstrated by a broad body of evidence from two large, diverse and comprehensive prevention trials, which included individuals such as racially diverse men who have sex with men, transgender women and Black cisgender women (22-24) who likely reflect populations in need of novel PrEP modalities. Implementation studies also show high persistence (25) and consistently high efficacy of cabotegravir for HIV prevention (99.6%–100%) across varied real-world

settings and populations (18, 26-33). Cabotegravir has been demonstrated to reach populations that have been underserved by oral PrEP implementation, including women, ethnic minority groups, and individuals who had not previously used or had discontinued oral PrEP (31). Addressing disparities in awareness, access, and uptake of primary prevention among different populations is key (6, 11). In England, there may also be regional diversities in unmet needs, with UKHSA data showing a rising number of new HIV diagnoses and sexually transmitted infections (STI) in North East England, with only 57% of North East residents with a PrEP need initiating or continuing PrEP (6, 34).

The provision of an alternative treatment modality/dosing regimen may better suit some individuals' needs or help to reduce barriers related to stigma or poor adherence (35, 36). For example, a recent UK study demonstrated that men who engage in sexual activity with both men and women value confidentiality and may avoid using oral PrEP due to discretion concerns; injectable PrEP offers discrete usage, providing an ideal option without need for disclosure (37). In other real-world United States (US) data, early adopters of cabotegravir for PrEP were commonly prior oral PrEP users with a clinical need or preference for non-oral PrEP, highlighting the need for alternative choices among people who use PrEP for HIV prevention (38).

Further efforts are clearly still required to end the HIV epidemic. Access to innovative interventions such as cabotegravir, alongside existing oral PrEP options, is critical to ensure that people in the UK at high risk of HIV acquisition can access and use effective HIV prevention strategies. This will not only help to enable achieving the UK's ambition of ending HIV transmissions by 2030 (4), but also avoid the significant downstream individual, societal, and economic burden associated with future HIV acquisitions.

NICE National Institute for Health and Care Excellence

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

ViiV additional evidence submission – 11th April 2025

ViiV comments

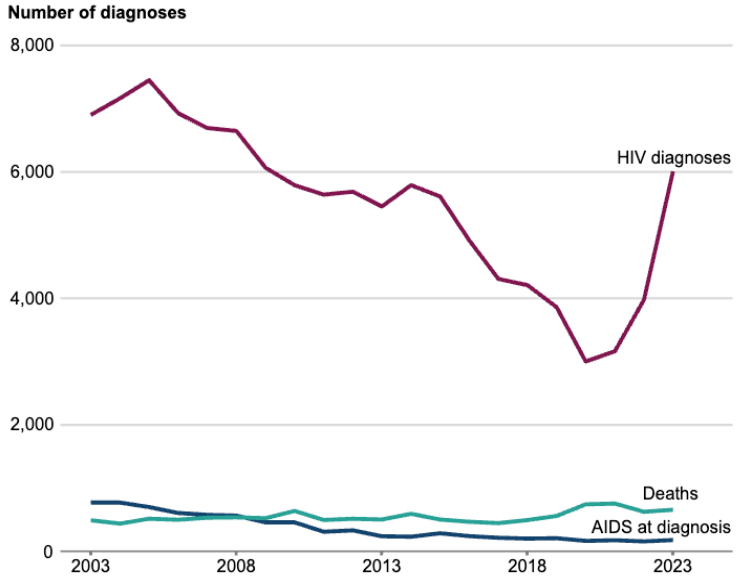
Table 1: ViiV comments and description of new evidence for uncertainties

Comment	
1. The baseline risk of HIV acquisition	**Key takeaways** **Factors affecting an individual's likelihood to be exposed to HIV are uniquely personal and multifactorial and can have an exceptional impact on the risk of HIV acquisition. There are significant limitations to all studies assessing risk of HIV acquisition especially in the population at high risk due to the personal and changing nature of HIV incidence.** **Considering the totality of relevant UK data and literature, incidence rates range from 3.9-17.4/100PYs in individuals at high risk of HIV not receiving PrEP. Therefore, 3.9/100 PYs is a reasonable and conservative assumption to inform the base case cost-effectiveness analysis.** **The planned UKHSA analyses could provide an additional source to complement the current literature. Clinical experts have shared the necessity for comprehensive scenario analyses exploring a variety of markers of high risk to address confounding or extraneous variables impacting the outcome. In addition, HIV diagnoses reported in both GUMCAD and HARS datasets are essential to include, to avoid underestimating the HIV incidence. This will be critical to ensure uncertainty is assessed and mitigated** **1. Evidence identified in available literature reporting HIV incidence in the UK** ViiV acknowledge the Committee's position that the baseline risk of HIV acquisition is a key uncertainty for the economic model. Due to risk of HIV acquisition being multifactorial, the high-risk population aligned with the cabotegravir indication

Comment	
	is heterogeneous and associated with significant variance with regard to incidence, as reported in the AURAH2 study and visually represented in Appendix B. Given many of the factors that may increase the likelihood of individuals being exposed to HIV are uniquely personal and can change over time with evolving life circumstances, database analyses and studies are imperfect in their ability to accurately assess high-risk incidence. That said as described by the clinical experts at the previous Committee meetings, HCPs with experience in prescribing PrEP are adept in their ability to identify individuals at high risk of HIV acquisition who would benefit from PrEP through their clinical reasoning and assessment. A comprehensive literature search has been conducted to identify baseline risk data relevant to the decision problem, with inclusion criteria as follows: • Population: Adults and adolescents at high risk of acquired HIV-1 acquisition as defined by the BHIVA/BASHH guidelines (39) (in line with the cabotegravir license). • Intervention: No PrEP • Outcomes: Incidence rate of HIV (e.g. x per 100 PYS) • Geography: UK or Western Europe Excluded studies that reported incidence of HIV but were not considered relevant to the decision problem or could inform the baseline incidence figure in the cost effectiveness model are summarised in Appendix D, with rationale for exclusion. *Please note, ViiV are currently undertaking a comprehensive formal systematic literature review to provide confidence in the identification of all relevant incidence data to the decision problem. The completion date of this study is yet to be determined. ViiV will ensure communication with the NICE team to allow for consideration by the Committee if timelines allow for inclusion into this health technology appraisal.* Given the challenges with incidence data collection, ViiV acknowledge that there are limitations in all available studies and data sources. Therefore, consideration of the totality of identified UK data for HIV incidence in populations for which cabotegravir is indicated highlights the range of incidence that is plausible, this is presented in Figure 3, Appendix B.

Comment	
	The UK incidence rates from the relevant literature range from 3.9–17.4/100 PYs in individuals at high risk of HIV acquisition not receiving PrEP. From 2005, the number of new HIV diagnoses were declining, most notably between 2015 and 2019. However, in recent years, the incidence of new diagnoses has increased, and is now at a similar rate to pre-2015 levels, continuing to rise (Figure 1). In addition, funding cuts to global HIV response programs are anticipated to lead to a resurgence of the epidemic, potentially resulting in millions more new HIV acquisitions, particularly among vulnerable populations (1). Due to migration and travel, this is likely to further increase the incidence of HIV within the UK over the coming years, as HIV testing has returned to pre-pandemic levels and emergency department opt-out testing is scaled up nationally (40).

Figure 1: HIV diagnoses, AIDS at diagnosis, and all-cause deaths in people with HIV, England, 2003 to 2023

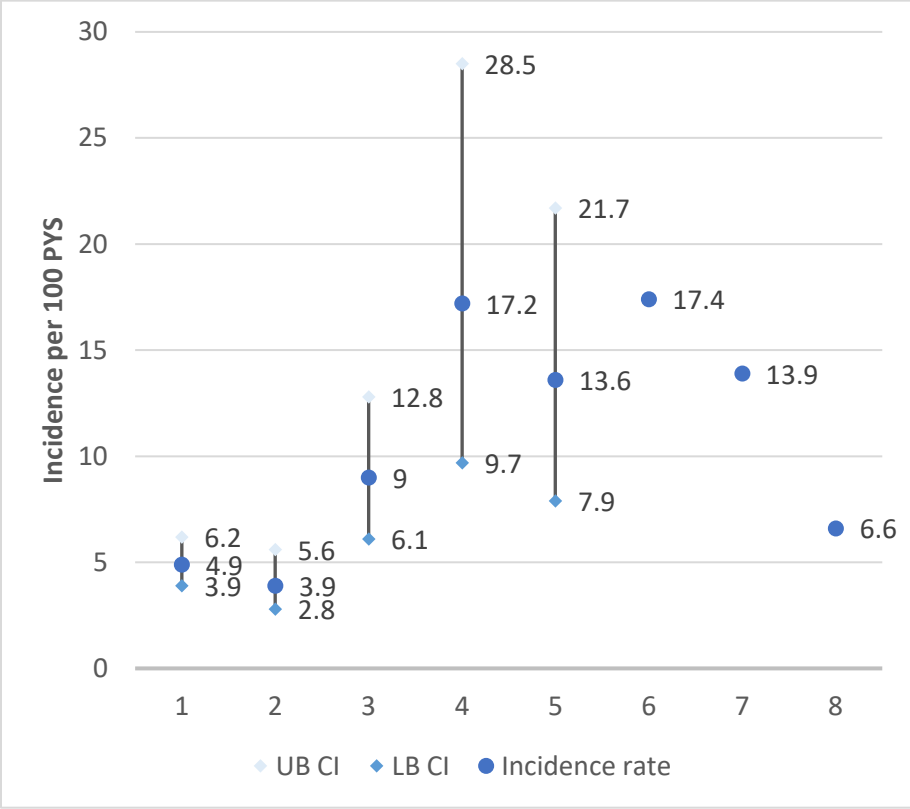


Source: Data from routine returns to the HIV and AIDS Reporting System (HARS) (New HIV diagnoses, AIDS, deaths and people in care in England of the accompanying data tables).

Source: UKHSA, 2024 (5).

Therefore, although there are clear limitations for the GUMCAD analyses, primarily using a singular marker of high risk, based on the totality of relevant evidence identified, ViiV continue to consider 3.9/100 PYs a reasonable assumption to inform the base case. Based on the literature, individuals within the high-risk population may have a significantly higher risk of HIV acquisition associated with their personal circumstances.

Figure 2: Incidence per 100 PYs according to analysis populations



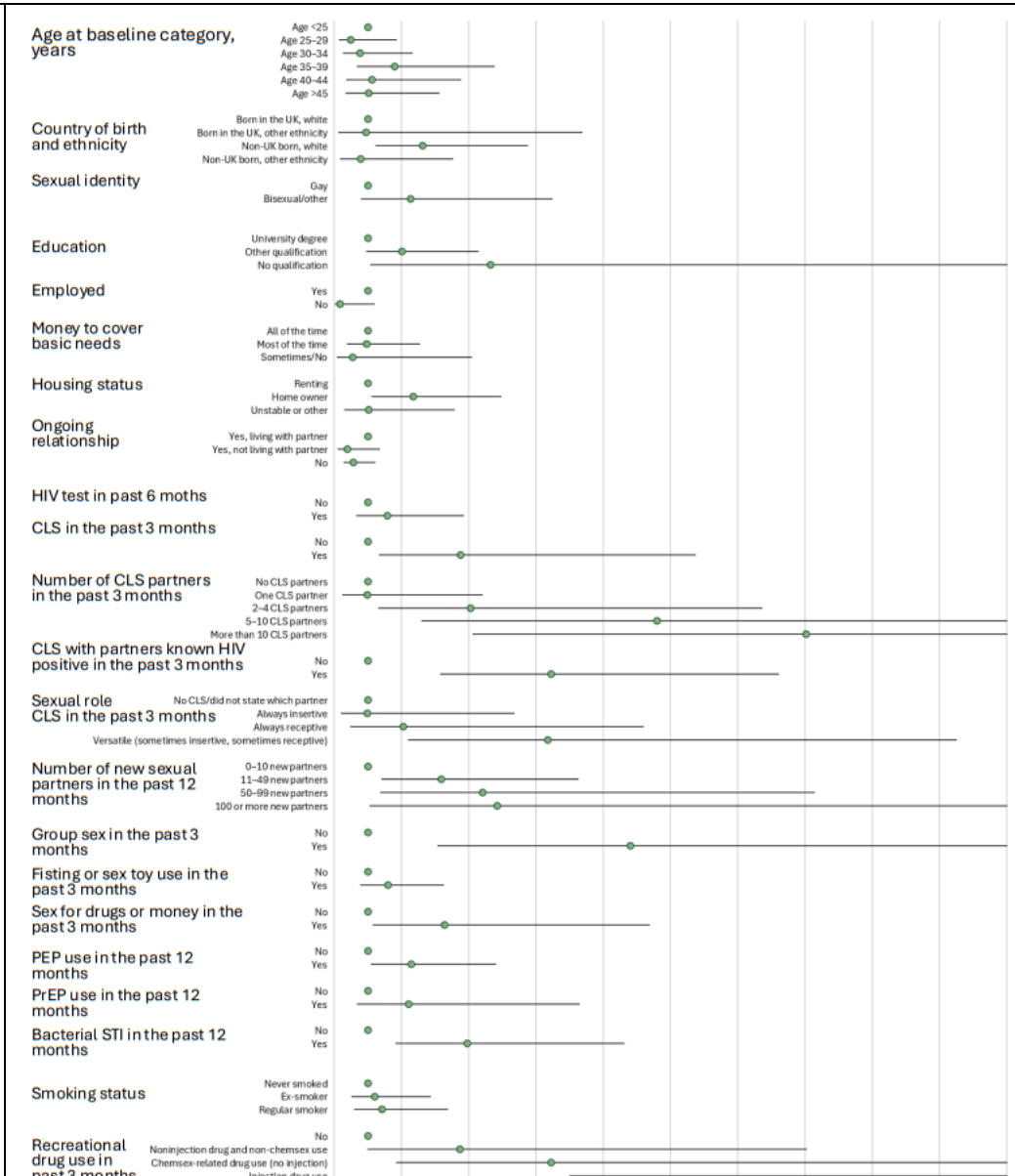
Study, year of data collection and analyses population:

1. GUMCAD 2014 recent rectal bacterial STI (39)
2. GUMCAD 2014 recent rectal bacterial STI and HIV test in previous 12 months (39)

Comment	
	3. PROUD 2012-2014 MSM SHS CLS last 90 days (41) 4. PROUD 2012-2014 MSM SHS CLS last 90 days + diagnosis of syphilis, CT or GC in past 12 months (41, 42) 5. PROUD 2012-2014 MSM SHS CLS last 90 days + receptive anal sex with ≥2 partners in past 3 months (41, 42) 6. PROUD 2012-2014 MSM SHS CLS last 90 days + rectal chlamydia or gonorrhoea in previous year (41, 42) 7. PROUD 2012-2014MSM SHS CLS last 90 days + unprotected receptive anal sex with two or more partners year (41, 42) 8. IPERGAY 2012-2016 MSM and trans women who reported anal sex with at least two sexual partners, without systematic condom use, in the previous 6 months (43) Note, the IMPACT study reported a clinically implausible, lower HIV incidence among non-PrEP users with a marker of high risk (e.g. rectal bacterial STI, PEP use) of 0.832/100 PY (95%: CI 0.761, 0.910] compared with those without a marker of high risk (2.076/100 PY [95% CI: 1.803, 2.390]) (44, 45) and therefore has been excluded. The use of PEP and the ability to self-source PrEP in the UK at that time, are likely to be confounders underestimating HIV incidence for individuals at high risk not on PrEP. *As highlighted above, ViiV are undertaking a systematic literature review (SLR) to identify all relevant evidence to the decision problem which report on baseline risk. Based on this SLR, ViiV are exploring the possibility of synthesising the evidence in collaboration with prominent UK evidence synthesis experts to provide additional confidence to the Committee.* **2. <u>Limitations associated with UK datasets reporting HIV incidence</u>** ViiV are aware that NICE and UKHSA are planning to conduct additional analyses to complement the available UK literature on incidence rates in those that are at high risk of HIV acquisition. At a recent UK advisory board, HIV and epidemiology experts [redacted] to inform the Committee's decision, as follows:

Comment	
	[redacted] **<u>Considerations for appropriate use of UK national surveillance datasets given limitations</u>** UK datasets available to estimate the baseline risk of HIV acquisition include: • GUMCAD (46): A mandatory sexual health database which collects data on STI tests, diagnoses, and services from all commissioned SHSs in England. Specifically, GUMCAD collects data on new HIV acquisitions diagnosed in SHSs, potential markers that may be considered for high risk, and PrEP-related data (PrEP need, PrEP need identified, PrEP initiated or continued). • HARS (47): A database reporting all new HIV diagnoses across any locations (SHSs, emergency departments [ED], primary/secondary/tertiary care). The database includes a question on previous PrEP use over a defined time interval. ***Populations in GUMCAD and HARS*** An important consideration for any analysis is that GUMCAD does not capture new HIV diagnoses outside of SHSs. A key strategy of the UK government is the rollout of opt-out blood-borne virus screening in EDs (48), and diagnoses in these other settings outside of SHSs are recorded by HARS. Ideally, linkage across the two datasets would allow for the inclusion of HIV acquisitions from any location. Expert feedback indicated that [redacted] Expert feedback indicated that [redacted]

Comment	
	[redacted] There may be other limitations associated with GUMCAD, with an expert at the advisory [redacted]. During the PROUD study in England, the overall incidence derived from 2012 data amongst men having sex with men attending SHSs was 1.34/100 PY (49), whereas the incidence in PROUD in the deferred arm of the PROUD trial was seven times higher (9.0/100 PY [90% confidence interval [CI]: 6.1, 12.8]) (41). National surveillance incidence data will include populations with variable levels of risk (i.e. not all of the population included will be PrEP eligible) and usage of existing biomedical interventions (e.g. PEP), versus data from trial populations with criteria selecting for PrEP need. This variance identifies potential limitations in national surveillance incidence reporting compared to targeted trial populations, signalling that not all those included in surveillance systems will be the target population for PrEP and include people with variable levels of risk. This suggests that defining the population at high risk and mitigating potential discrepancies is crucial. The expert also noted that [redacted] ***Variables collected in GUMCAD and HARS*** Based on the variables reported by each dataset, while both can be used to evaluate the outcome (new HIV diagnoses), it is more likely that GUMCAD data can be used to evaluate the population at high risk of HIV acquisition who are not on PrEP. It should be noted that behavioural risk factor data in GUMCAD are mostly limited to sexual partners, with limitations in behavioural data availability (including drug and alcohol use), and are therefore imperfect in identifying a complete eligible population. For a full list of GUMCAD reported variables, and a list of GUMCAD variables shared with HARS, see


Age at baseline category, years
Age <25
Age 25-29
Age 30-34
Age 35-39
Age 40-44
Age >45
Country of birth and ethnicity
Born in the UK, white
Born in the UK, other ethnicity
Non-UK born, white
Non-UK born, other ethnicity
Sexual identity
Gay
Bisexual/other
Education
University degree
Other qualification
No qualification
Employed
Yes
No
Money to cover basic needs
All of the time
Most of the time
Sometimes/No
Housing status
Renting
Home owner
Unstable or other
Ongoing relationship
Yes, living with partner
Yes, not living with partner
No
HIV test in past 6 moths
No
Yes
CLS in the past 3 months
No
Yes
Number of CLS partners in the past 3 months
No CLS partners
One CLS partner
2–4 CLS partners
5–10 CLS partners
More than 10 CLS partners
CLS with partners known HIV positive in the past 3 months
No
Yes
Sexual role CLS in the past 3 months
No CLS/did not state which partner
Always insertive
Always receptive
Versatile (sometimes insertive, sometimes receptive)
Number of new sexual partners in the past 12 months
0–10 new partners
11–49 new partners
50–99 new partners
100 or more new partners
Group sex in the past 3 months
No
Yes
Fisting or sex toy use in the past 3 months
No
Yes
Sex for drugs or money in the past 3 months
No
Yes
PEP use in the past 12 months
No
Yes
PrEP use in the past 12 months
No
Yes
Bacterial STI in the past 12 months
No
Yes
Smoking status
Never smoked
Ex-smoker
Regular smoker
Recreational drug use in
No
Noninjection drug and non-chemsex use
Chemsex-related drug use (no injection)

Comment	
	Source: Hanum et al, 2021 (50). Appendix C. ***Identifying markers of high risk in the UK national surveillance datasets*** Identifying an appropriate marker to stratify individuals at high risk of HIV acquisition represents a significant challenge due to variations in demographic groups, sexual behaviour and other multifactorial influencers to risk. Therefore, it is critical to consider scenario analyses exploring different markers or combination of markers to reduce uncertainty. **Identification and limitations in identification of the most suitable marker(s) of high risk** Markers in England were evaluated by the AURAH2 study (50). Results indicated higher incidence rates among men that have sex with men with no educational qualification (2.64/100 PY), more than 10 condomless anal sex partners (3.36/100 PY), recent condomless sex with an HIV-positive partner (2.63/100 PY), and injecting drug use (4.74/100 PY). These findings highlight varying incidence rates based on different high-risk markers (50). This study also identified that despite declines in HIV incidence, rates remained high among men who reported injection drug use, chemsex drug use, condomless sex with multiple partners, and group sex (50), providing additional insights towards potentially useful makers for stratifying individuals at high-risk of HIV acquisition. However, a UK expert stated that there are [redacted] This is highlighted by results from the IMPACT trial, which reported a clinically implausible, lower HIV incidence among non-PrEP users with a marker of high risk (e.g. rectal bacterial STI, PEP use) of 0.832/100 PY (95%: CI 0.761, 0.910] compared with those without a marker of high risk (2.076/100 PY [95% CI: 1.803, 2.390]) (44). This reflects limitations of using rectal gonorrhoea as a proxy for HIV incidence, given the complex and context-dependent nature of HIV exposure risk (51), and the impact of PEP to HIV following sexual exposures (PEPSE) on reducing HIV acquisition (52) and contributing to reducing the incidence of HIV (53). It was also highlighted by an expert that [redacted]. This, combined with limited data availability of behavioural risk factors in GUMCAD and limitations in the systematic reporting of other indicators such as number of

Comment	
	sexual partners and chemsex use (54), may also contribute to the clinically implausible lower incidence reported among individuals with markers of high risk. Experts felt that [redacted] (16). An expert stated that [redacted]. While there is already existing literature around defining multiple markers of high risk for HIV acquisition, taken together, data from AURAH2 and IMPACT clearly show that when estimating HIV incidence among the high-risk population, it is important to consider that using a single marker may not adequately stratify the population and could lead to an underestimation of the true incidence for the population relevant to the decision problem. Considering scenarios with a range of markers may help mitigate this potential effect. **Scenario analyses to consider** To facilitate further discussions and enable the Committee to agree on appropriate analyses, ViiV submitted a letter on April 1st, 2025, outlining potential limitations and suggestions for UKHSA to consider. ViiV recommends scenario analyses to generate a range of values for the baseline risk of HIV acquisition in people at high risk of HIV who are eligible for PrEP but not taking it (Appendix A). Scenario analyses are essential for quantifying the heterogeneity and uncertainty associated with this critical parameter in economic modelling. The list of suggestions for the UKHSA analyses, while not exhaustive, are provided below:

Comment	
	Markers of high risk *(The suggested list of variables is non exhaustive, and ViiV welcome additional scenarios using alternative markers to be explored)* • Recent STI history (bacterial STI, bacterial rectal STI) • Sex partner factors (number of sexual partners in last 6 months, condomless sex) • Clinical indication of PrEP eligibility • Alcohol and drug use (noting limitations regarding data quality of these variables in GUMCAD). ***PEPSE usage*** Recent use of PEPSE may be considered a marker of high risk. However, for the purpose of this analysis, it may be a confounder, leading to lower incidence as a result of PEP effectiveness in preventing HIV (52, 53). We recommend exploring scenarios that censor the use of PEP from the incidence estimates. Recent use of PEPSE may be considered a marker of high risk. However, for the purpose of this analysis it may be a confounder, leading to lower incidence as a result of PEP effectiveness in preventing HIV (52, 53). We recommend exploring scenarios that censor the use of PEP from the incidence estimates. ***HIV diagnoses*** To estimate the baseline risk, the 'denominator' (i.e. population at high risk not on PrEP) will be dependent on the sampling frame and the resulting populations included. The 'numerator' (i.e. individuals who acquired HIV) will also be dependent on the definitions applied for inclusion of an HIV acquisition. Scenario analyses may present changes to both the incidence of HIV acquisitions (the 'numerator') and the population based on markers of high risk (the 'denominator'). ViiV recommends that the impact of including and excluding each high-risk marker in turn (the denominator) is combined with alternative scenarios to capture HIV acquisitions, which will result in a comprehensive set of alternative analyses. A comparison of HIV acquisitions in GUMCAD versus HARS is necessary to ensure the capture of new HIV diagnoses, beyond just those attending SHSs, to more accurately estimate the incidence for all people at high risk.

Comment	
2. The population who would access cabotegravir in practice, and how that relates to the baseline risk	**Key takeaway: There is likely to be higher HIV incidence among people for whom oral PrEP is not appropriate. It is not feasible to estimate the HIV incidence in this population due to lack of data granularity. Therefore, HIV incidence of those of high risk (who could receive cabotegravir) is likely to be underestimated with the analysis using existing datasets.** ViiV maintain the expectation that in clinical practice, cabotegravir will predominantly be used by people at high risk of HIV acquisition for whom oral PrEP is not appropriate. This is in line with the population cabotegravir is recommended for by the Scottish Medicines Consortium (55). Notably, as these people remain at high risk of HIV acquisition and do not have any suitable biomedical HIV prevention options, the incidence of HIV acquisition among this population will likely be higher than those for whom oral PrEP is suitable. At the 2025 advisory board, experts were also [redacted] (16). The reasons provided by experts were that [redacted]. The different baseline risk among different groups of people at high risk (e.g. does not or cannot take oral PrEP, sub-optimal adherence to oral PrEP, optimal adherence to oral PrEP) cannot be quantified due to limited granularity in existing data sets. Therefore, it is important to acknowledge that the incidence generated will underestimate the incidence in the population in which cabotegravir will be used.

3. The impact of cabotegravir on persistence with PrEP therapies	**Key takeaway: Long-acting injectable interventions provide persistence advantages over oral interventions, including PrEP. This is supported by multiple sources of evidence from RWE.** Based on newly available data, ViiV considers the 20% persistence advantage value to be a conservative estimate in the economic model. **RWE supports high levels of persistence with cabotegravir** • In the OPERA cohort of routine clinical care in the US (N=764 cabotegravir users), at median of 10 months (interquartile range [IQR]: 7–13) follow-up, 81% of individuals were still receiving cabotegravir at the end of the analysis†,§ (26) • In the TRIO cohort, the 2-year analysis‡ demonstrated that 83% (393,474) of individuals remained on cabotegravir at a median follow-up of 7 months (IQR: 3–14) after first injection (27) • An implementation study in a large safety-net primary care centre in Southern US for individuals referred to the cabotegravir PrEP programme between 1st December 2022–1st August 2023, with outcomes assessed through 1st December 2023 reported 90% persistence with cabotegravir among 77 initiators¶ (56) • In a study of adults receiving PrEP during December 2021–June 2024 in Kaiser Permanente, Northern California, of the 141 cabotegravir users, 78.3% and 73.0% persisted on cabotegravir at 28 and 60 weeks following initiation, respectively (31) • In the PILLAR cohort, at Month 6 and Month 12, persistence on cabotegravir was 85% (n=171/201) and 72% (n=142/196; excludes 5 participants who completed the study post data cut-off) (25) • In the Brazilian ImPrEP study, cabotegravir significantly improved coverage and protection (18). • In the CAN community health network of 26 outpatient clinics in the US, persistence was 81.3% (n=126/155) among cabotegravir users receiving ≥ 1 injection (57). RWE has also demonstrated that a high proportion of individuals discontinue oral PrEP across a range of countries, including the US, France and Belgium, with persistence lower than reported in globally conducted clinical trials (58-60) (CITE). In the Brazilian ImPrEP study, of the 3,780 individuals with ≥1 follow-up visit, 66% discontinued oral PrEP during follow-up (61). In a US study, median duration of TDF/FTC (n=24,232) use was 220 days (IQR: 80–511) and persistence

	was 79.4% at 3 months, 70.2% at 6 months, declining to 57.4% at 12 months among individuals with ≥6 months (n=18,261) and ≥12 months (n=12,667) follow-up (58). In another US study, less than half of new oral PrEP users persisted beyond 6 months (42.4% of 183,584 new users in 2017–2018, and 37.9% of 321,224 new users in 2021–2022 (62). A global systematic review and meta-analysis, which included studies published up to December 2020, also reported a substantial proportion of oral PrEP users discontinued use, with a pooled discontinuation rate of 41.0% (95% CI: 18.8, 63.5) globally (16 studies) and 17.4% (95% CI: 13.0, 22.9) in Europe (6 studies) within 6 months of PrEP initiation (63). The high levels of discontinuation observed with oral PrEP highlights the need for alternative modalities. In the recent advisory board, experts were asked [redacted] (16). The clinical experts agreed [redacted]. They suggested that [redacted]. The US study called ABOVE compared real-world adherence and persistence with long-acting cabotegravir plus rilpivirine with oral antiretroviral therapy (ART) among people living with HIV (64). This demonstrated that in individuals receiving stable ART, compared with remaining on oral ART, switching to long-acting cabotegravir plus rilpivirine resulted in significantly higher adherence (72% vs 43%, p<0.001) and persistence (274 vs 256 days, p<0.001). An expert also expressed [redacted](16). Evidence of improved persistence of injectable treatments compared with oral therapies is available for other health conditions including the treatment of Type 2 diabetes, whereby in a real-world setting, once-weekly injectable GLP-1 receptor agonists were associated with better adherence and persistence compared with daily regimens over 1 year (65). In patients with schizophrenia or bipolar disorder, patients receiving long-acting injectables were 20% less likely to discontinue their medication during the entire follow-up period (≥365 days) than those who changed to oral antipsychotic monotherapy (66). A systematic review and meta-analysis of cohort studies investigating adherence and persistence to long-acting injectable dopamine receptor blocking agent therapy in the US reported the cumulative benefit of being persistently on the long-acting therapy was 1.65 times higher compared with the oral agents-exposed group (67).

Comment	
	Taken together, multiple sources of evidence support ViiV's position that there is an improvement in persistence with cabotegravir over oral PrEP, and that the 20% value is a conservative estimate. Footnote: Inclusion criterion ≥1 cabotegravir injection between †21st December 2021–30th June 2023; ‡December 2021–January 2024; §19% (124/646) of complete initiators who missed ≥2 target windows (i.e. ≥128 days without injection); ¶10% discontinued cabotegravir.
4. The percentage of people who switch from cabotegravir to oral PrEP	**Key takeaway: ViiV maintain that [redacted] transition to TDF/FTC after discontinuing cabotegravir is reasonable, considering additional RWE.** ViiV maintain that in the economic model, including some patients transitioning from cabotegravir to TDF/FTC represents the use of an alternative (not long-acting) PrEP modality in the pharmacokinetic tail. This is in line with the recommendation provided in the summary of product characteristics (SmPC), which states: "*Residual concentrations of cabotegravir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer); therefore, the prolonged release characteristics of Apretude (cabotegravir) injection should be taken into consideration when the medicinal product is discontinued and alternative not long-acting forms of PrEP are taken, as long as or at any time the risk of acquiring HIV is present in the months after discontinuation of Apretude*" (68). RWE has also shown that some individuals transition from cabotegravir to oral PrEP. • A Peer Specialist-Led Program in Washington DC has reported that 93% (27/29) of the individuals who discontinued cabotegravir and remained at risk for HIV were transitioned to oral 2-1-1 or daily PrEP (7% [2/29] were lost to follow up after five attempts to contact them) (69).

Comment	
	• In two large integrated healthcare systems in the US from 23rd May 2022 through 30th June 2024, among 23,311 PrEP users, 180 were prescribed cabotegravir for PrEP. Thirty-five individuals discontinued cabotegravir for PrEP; 12 had oral PrEP prescribed after discontinuation (31) • A multicentre, pilot implementation study of CAB-LA in Zambia was conducted across six sites in two districts in a real-world setting. Participants were ≥16 years of age and at risk of HIV who anticipate being on PrEP for 12 months. A total of 609 participants were included and 3.9% (n = 24) discontinued cabotegravir injections. Most participants switched to oral PrEP at discontinuation (92%; n = 22) (70). At the recent advisory board, experts were asked to comment on whether [redacted] (16). [redacted]. Based on the available RWE and expert feedback, ViiV maintain that it is reasonable to assume that [redacted]% of people who are high risk of HIV acquisition transition to TDF/FTC after discontinuing cabotegravir.
5. The duration of the high-risk period	**Key takeaway: ViiV maintain that an assumption of 5-years for the duration of high-risk period is most appropriate, and that 10 years is too long. This has been supported by RWE of persistence and by clinical experts and stakeholders throughout the appraisal.** The draft guidance notes that clinical expert opinion heard at the first ACM explained that "there are multiple components that define HIV risk and most of them do not stay constant over time, so [the expert] considered that 5 years is a more appropriate estimate for the at-high-risk period of HIV acquisition" (71).

Comment	
	ViiV's decision to select the 5-year duration of elevated risk was informed by real-world evidence of persistence to TDF/FTC. These data demonstrated a high rate of discontinuation of TDF/FTC (over 40% of people at 12 months) (72), and extrapolation of the real-world persistence data in the economic model leads to a decreasing proportion of individuals on PrEP and an increasing proportion of individuals on no PrEP over time, so that in both the TDF/FTC and cabotegravir arms, the proportion of individuals who remain on PrEP after 5 years is 15% or lower. In support of this, additional RWE has become available, which also demonstrated high levels of discontinuation with oral PrEP (66%) in the ImPrEP study (61) between February 2018 to July 2024. ViiV maintain that considering an extended period of elevated risk in the economic model, where most individuals have discontinued their PrEP modalities, is not appropriate for comparing the cost-effectiveness of PrEP options. The aforementioned clinical opinion, and the real-world evidence on persistence supports an assumption that typical durations of elevated risk are unlikely to be longer than 5 years and may well be shorter. At the recent UK advisory board, experts explained that [redacted] (16). However, [redacted] (16). [redacted]. ViiV acknowledges there is some uncertainty in the estimation of the high-risk period but all evidence, including expert opinion, converges towards a 5-year or lower high-risk period.
Conclusion	In conclusion, after consideration of the totality of relevant evidence available and identified currently, ViiV continue to consider 3.9/100 PYs a reasonable assumption to inform the incidence rate in the model base case. The UKHSA analyses planned will add to the literature available. For these analyses, UK clinical and epidemiology experts have strongly recommended that [redacted]

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	[redacted]. This approach aims to reduce data limitations and uncertainties. ViiV have also provided compelling additional RWE to support the original base-case assumptions used in the economic model related to improved persistence with cabotegravir, the proportion of people transitioning to TDF/FTC after discontinuing cabotegravir, and the duration of the high-risk period. Recent international funding cuts have drastically changed projections of global HIV acquisitions (1), and this will have an impact on patients within the UK. Even before these recent aid policy changes, the UK was already projected to miss the UK HIV Action Plan's target of zero new HIV transmissions by 2030 (4, 7). To protect the health of those who live in the UK and to eradicate new HIV transmissions by 2030, urgent and increased efforts are imperative. ViiV appreciate the opportunity to submit further evidence, and hope that the commentary provided addresses some of the remaining points to help the Committee to make a recommendation on cabotegravir for the prevention of HIV-1 in people at high risk of HIV acquisition.

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Appendix A: Letter submitted to the UKHSA on 1st April 2025

ViiV Healthcare comments on baseline risk of HIV acquisition to support NICE appraisal request for evidence generation

1. Introduction

ViiV acknowledges concerns from the recent NICE Committee meeting on Cabotegravir for preventing HIV-1 [ID6255], specifically regarding baseline risk of HIV acquisition. NICE has requested more data from stakeholders, including the UK Health Security Agency (UKHSA) to be submitted by 11th April 2025. ViiV aims to collaborate with UKHSA to help ensure the data is accurate for a thorough appraisal.

2. Objectives

This document aims to highlight anticipated limitations in estimating HIV incidence among people at high risk not on PrEP and propose scenario analyses for UKHSA to consider. The limitations have been identified through an advisory board with UK experts in HIV and epidemiology, and that report will be submitted to NICE as evidence by 11-Apr-2025. Key limitations identified by UK experts include [redacted]

3. Description of limitations

There are known limitations to estimating incidence of HIV, most notably that incidence is rarely measured prospectively in cohorts with access to prevention services (1). We aim to identify additional limitations:

- **Stratifying Risk among People not on PrEP**
  With the availability of oral PrEP in the clinical pathway, it is essential to distinguish between individuals at high risk not on PrEP and the broader population. This distinction is necessary to avoid including individuals not at high risk and therefore with low PrEP need, which could significantly underestimate the true baseline incidence among those at high risk of HIV acquisition who are not on PrEP.
- **Markers of High Risk**
  Identifying appropriate markers to stratify individuals at high risk of HIV acquisition remains a significant challenge due to variations in demographic groups and sexual behaviour. This was underscored by the findings from the IMPACT Trial, which reported a paucity of key markers of higher risk in current surveillance data (2). The trial observed a clinically implausible lower HIV incidence among non-PrEP users with markers of high risk (such as rectal bacterial sexually transmitted infections or post-exposure prophylaxis use) [0.832/100PY (95%CI 0.761–0.910)] compared to those without markers of high risk [2.076/100PY 995%CI 1.803–2.390) (3). This reflects the known limitations of using rectal gonorrhoea as a proxy for HIV incidence, given the complex and context-dependent nature of HIV exposure risk (4), and the impact of post-exposure prophylaxis to HIV following sexual exposures (PEPSE) on reducing HIV acquisition (5) and contributing to reducing the incidence of HIV (6). Alternative markers have been evaluated in England, where

higher incidence rates were observed among men that have sex with men with no educational qualification [2.64/100PY], more than 10 condomless anal sex partner [3.36/100PPY], recent condomless sex with an HIV-positive partner [2.63/100PY], and injecting drug use [4.74/100PY], demonstrating the wide diversity in incidence based on different high-risk markers (7). This study also identified that despite declines in HIV incidence, rates remained high among men who reported injection drug use, chemsex drug use, condomless sex with multiple partners, and group sex (7), providing additional insights towards potentially useful makers for stratifying individuals at high-risk of HIV acquisition.

It is therefore imperative that any estimation of HIV incidence among individuals at high risk considers that a single marker may not suffice to stratify the population accurately and may underestimate the true incidence. Scenarios considering a range of markers might mitigate for this potential effect.

- **Variance between Trial Data and National Surveillance**
  Higher HIV incidence has been observed in PrEP trial comparison group populations including PROUD (8) and Ipergay trials which also compared incidence to national surveillance reporting. During the PROUD study in England, the overall incidence derived from avidity assay data amongst men having sex with men attending sexual health services was 1.34/100PY (10), whereas the incidence in PROUD in the deferred arm of the PROUD trial was seven times higher [9·0/100PY, 90%CI 6·1–12·8] (8). National surveillance incidence data will include populations with variable levels of risk (i.e. not all of the population included will be PrEP eligible) and usage of existing biomedical interventions (e.g. PEP), versus data from trial populations with criteria selecting for PrEP need. This variance identifies potential limitations in national surveillance incidence reporting compared to targeted trial populations, signalling that not all those included in surveillance systems will be the target population for PrEP and include people with variable levels of risk. This suggests that defining the population at high risk and mitigating potential discrepancies is crucial.
- **Populations within National Surveillance Datasets**
  An important consideration for any analysis is that the Genitourinary Medicines Clinic Activity Dataset (GUMCAD) (11) does not collect data of new HIV diagnosis outside of sexual health services; a key strategy of the UK government with the rollout of opt-out blood-borne virus screening in emergency departments (12). The HIV and AIDS Reporting System (HARS) (13) collects data on all new HIV diagnoses across various locations. Ideally, linkage across the two datasets would allow for the inclusion of HIV acquisitions from any location. In the absence of such linkage, comparing HIV acquisitions in GUMCAD versus HARS could be used to derive a population-specific scaling factor to account for HIV acquisitions not captured in GUMCAD.

4. Scenario analyses to consider

ViiV kindly suggests that, where practical, UKHSA presents a comprehensive set of scenario analyses for the baseline risk of HIV acquisition in those at high risk of HIV acquisition who would be eligible for PrEP, yet not currently using PrEP, to inform the background HIV incidence (no PrEP) used in the cost-effectiveness model analysis. This will help to quantify the heterogeneity and uncertainty around this key parameter for the economic modelling, as well as enabling the NICE expert reviewers and Committee to discuss and agree the most appropriate analyses that will inform their decision making. The points above highlight key limitations and considerations for this analysis, which should help inform which scenario

analyses should be run. Further suggestions are provided below, but are not exhaustive, and there may be other analyses that UKHSA believes it is helpful to submit.

Markers of high risk

(the suggested list of variables is non exhaustive, and we welcome additional scenarios using alternative markers to be explored)

- Recent STI history (bacterial STI, bacterial rectal STI)
- Sex partner factors (number of sexual partners in last 6 months, condomless sex)
- Clinical indication of PrEP eligibility
- Alcohol and drug use (noting limitations regarding data quality of these variables in GUMCAD)
-

PEPSE usage

Recent use of post-exposure prophylaxis for HIV following sexual exposures (PEPSE) may be considered a marker of high risk however, for the purpose of this analysis it may be a confounder leading to lower incidence as a result of PEP effectiveness in preventing HIV. We recommend exploring scenarios that censor the use of PEP from the incidence estimates.

HIV diagnoses

- A comparison of HIV acquisitions in GUMCAD versus HARS

Scenario analyses may present changes to both the incidence of HIV acquisitions (the 'numerator') and the population based on markers of high risk (the 'denominator'). We recommend that the impact of including and excluding each high-risk marker in turn (the denominator) is combined with alternative scenarios for the numerator, which will result in a comprehensive set of alternative analyses.

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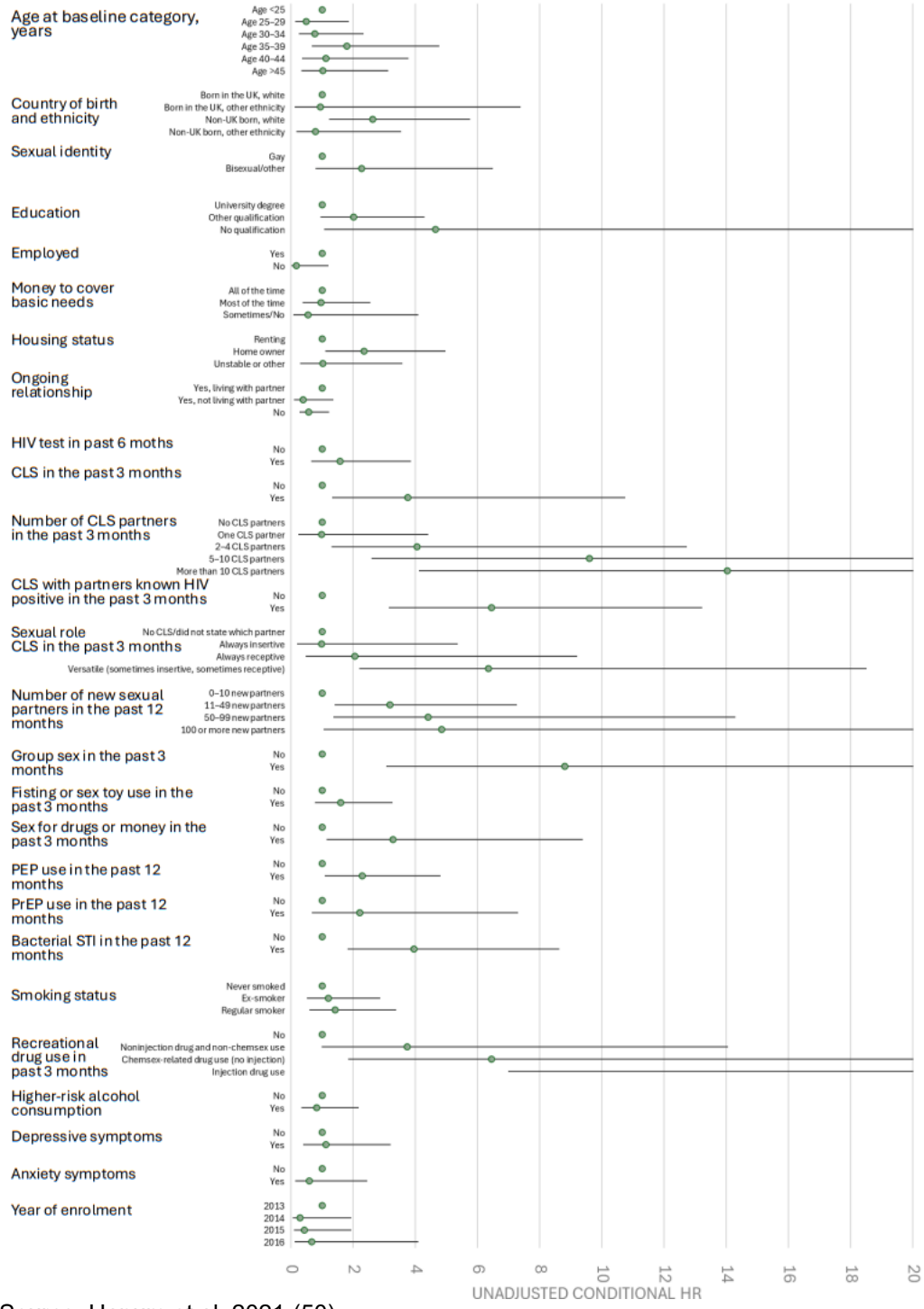
Appendix B: Variance of incidence

Figure 3: A visual representation adaptation of data to show the variance of incidence depending on markers of risk across demographic, socioeconomic, partner, sexual behaviour and health and lifestyle characteristics



Source: Hanum et al, 2021 (50).

Appendix C: Variables captured in the relevant datasets

C1. Variables captured in GUMCAD

Variables reported in GUMCAD include (73):

- Clinic ID
- Clinic type
- Patient ID
- Patient type (prisoner, active sex worker)
- Gender identity
- Sex at birth
- Age
- Sexual orientation
- Ethnicity
- Country of birth
- Patient residence (local authority as managed by ONS)
- Consultation referral (GP, self-referral)
- Consultation date
- Consultation medium (face-to-face, online, telephone)
- Consultation type (new, follow-up)
- Consultation speciality (STI, STI and HIV, STI and SRH, SRH, HIV)
- Consultation via partner notification (yes/no)
- Consultation symptomatic (yes/no)
- Diagnosis confirmed
- Diagnosis site (genital, ocular, pharyngeal, rectal, other)
- Diagnosis treated (yes/no)
- **Sex partners** *[different risk to orientation]* (sex partners, new sex partner, condomless sex, vaginal sex, anal sex [insertive/receptive], oral sex, genital area, opposite sex partners [number, new, and condomless in past 3 months] and same sex partners [number, HIV positive, condomless receptive/insertive, condomless receptive in past 3 months]
- Partner notification
- **PrEP eligibility**[1] (what is the patient's eligibility for being offered PrEP), uptake (outcome of offer of PrEP), regimen, prescription, stop reason
- Alcohol and drug use (including chemsex, injecting drugs, sharing drug injecting equipment)

[1] It is only necessary to provide answers to questions which are relevant to the patient consultation. If the patient has not been assessed for PrEP it is not necessary to answer these questions, they should therefore be reported as 'Not applicable'. PSS default data entry to 'Not applicable' for unanswered questions.

Note, 2019 onwards included sexual behavior, alcohol and recreational drug use, outcomes of partner notification, the provision of PrEP, SNOMED chlamydia STI surveillance coding.

C2. GUMCAD variables shared with HARS

A list of GUMCAD variables shared with HARS is provided in Table 2 (73).

Table 2: List of GUMCAD variables shared with HARS

GUMCAD	HARS
ClinicID	Org_ID
PatientID	Patient ID
Gender_Identity	Gender_Identity
Gender_Birth	Gender_Birth
Ethnicity	Ethnicity
Country_Birth	Country_Birth
LSOA	LSOA
Consultation_Date	HIVCare_Date
Consultation_Medium	Consultation Medium used
New HIV diagnosis	
Episode_Activity (codes: H1, H1A, H1B)	Dx_UK_Date (HIV diagnosis date in the UK)
HIV-related Care	
Episode_Activity (codes: H2)	HIV_care_date (Consultation date for HIV care)
Patient characteristics	
Patient_Type - sex_worker	Sex_worker
Patient_Type - Prisoner	Prisoner

Source: UKHSA 2021 (73).
Abbreviations: GUMCAD, Genitourinary Medicines Clinic Activity Dataset; HARS, The HIV and AIDS Reporting System; HIV, human immunodeficiency virus; UK, United Kingdom.

Appendix D: Literature search

Excluded studies that reported incidence of HIV but were not considered relevant to the decision problem (74) are presented in Table 3.

Table 3: Excluded studies that reported incidence of HIV but were not considered relevant to the decision problem

Data Source	Citation	Year(s) Represented	Location	Population	Rationale for exclusion
IMPACT (45)	Sullivan (2023)	2017 to 2020	England	MSM SHS attendees, trial participants	Overall population not high risk and use of oral PrEP. Note, "high risk" group exclusion rational included in main body of response.
GUMCAD (45)	Sullivan (2023)	2017 to 2020	England	MSM SHS attendees, non-trial participants	Not a high-risk population
Global Pooled Analysis (75)	Landovitz (2024)	2011 to 2019	28 countries	Cisgender men, Cisgender women, and transgender women, low adherence to TDF/FTC (<2 doses/week)	UK/Western Europe data & high-risk subgroups not reported
Global Burden of Disease (76)	Carter (2024)	1990 to 2021, with forecasts to 2050	204 countries and territories	High income (2021)	UK & high-risk subgroup not reported.
AURAH2 (50)	Hanum (2021)	2019 to 2019	England (London and Brighton)	GBMSM	Significant use of PrEP and PEP. Therefore, not representative of a population not receiving PrEP
HVTN 706Cite (2023) (8, 77, 78)	Beyrer (2024)	2019 to 2022	Europe, Latin America, and North America	MSM and transgender people who have sex with men	Western Europe subgroup not reported.

NICE National Institute for Health and Care Excellence

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]
Addendum to ViiV additional evidence submission – 16th April 2025

Executive summary

This addendum supports ViiV Healthcare's (ViiV's) additional evidence submission to the National Institute for Health and Care Excellence (NICE) on the 11th April 2025. This addendum presents newly available data on treatment persistence, in addition to [redacted]. This supplementary evidence, alongside a revised base case and cost-effectiveness analysis, is provided to aid the Committee in their evaluation for the appraisal of cabotegravir for the prevention of human immunodeficiency virus-1 (HIV-1) acquisition.

In summary, additional evidence highlights that a 20% persistence advantage for cabotegravir over tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is extremely conservative; [redacted] demonstrates [redacted] for [redacted]. Furthermore, the [redacted] when cabotegravir [redacted]. This reflects the approach taken in 98% of the population in a recent US analysis (1), in addition to expectations of approach in the UK.

Furthermore, ViiV maintains that the assumption of an HIV acquisition rate of 3.9/100 person years (PYs) to inform the cost effectiveness model base case incidence rate is appropriate. This rate is on the lower end of the range of incidence rates reported in the literature for the population of interest.

The additional evidence on cost-effectiveness confirms previous analyses provided by ViiV: cabotegravir offers consistent and robust value in people at high risk of HIV acquisition; in the base case and all scenarios cabotegravir was dominant compared to TDF/FTC and no PrEP.

Ensuring access to innovative interventions such as cabotegravir, alongside existing oral PrEP options, is vital to support people in the UK at high risk of HIV acquisition in accessing and using effective prevention strategies. These strategies are key not only to achieving the UK's goal of ending HIV transmission by 2030 (2), but also to advancing person-centred PrEP provision (3) and reducing the substantial individual, societal, and economic burden associated with future HIV acquisitions.

1. Background on addendum

ViiV has since obtained further evidence that is relevant to key areas of uncertainty in the appraisal. Specifically, this evidence addresses persistence, a key uncertainty raised following the second Committee meeting, in addition to efficacy data from an [redacted] included in ViiV's original submission (February 2024). ViiV therefore welcomes the opportunity to present this supplementary evidence, alongside a revised base case, for the Committee's consideration.

ViiV remains committed to supporting a robust and transparent appraisal process and would be pleased to respond to any questions or requests for further clarification from the Committee regarding the content of this addendum.

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]
Addendum to ViiV additional evidence submission – 16th April 2025

2. Summary of the revised ViiV's base case

Table 1 provides a summary of the changes made to the company's base case cost-effectiveness analysis compared with the previous submission in response to draft guidance (October 2024).

Table 1: Summary of the revised ViiV's base case

Parameter	Previous value	New value	Justification
Baseline risk	Men who have sex with men and transgender women based on UK literature identified (GUMCAD 2014) (4) • 3.9/100 PYs Cisgender women based on incidence estimate from ITC • [redacted]/100 PYs	Men who have sex with men and transgender women based on UK literature identified (GUMCAD 2014) (4) • 3.9/100 PYs Cisgender women based on incidence estimate from [redacted] • [redacted]/100 PYs	Evidence in literature support high variability of incidence reported in the population of interest (range from 3.9 to 17.4/100 PYs). Therefore, considering this range, the previous assumption of 3.9/100 PYs is reasonable as it is the lowest of the relevant estimates across literature in the relevant population. A detailed description of available evidence is presented in the evidence submitted on April 11th (comment 1 and Appendix C). The incidence for the cisgender women cohort in the model was updated to reflect [redacted] (see section 4)
Persistence [redacted]	Assumed +20% improvement (% people on PrEP at [redacted]): • CAB: [redacted] and [redacted] • TDF/FTC: [redacted] and [redacted]	Maintain original, conservative positioning of +20% improvement with scenario analysis using persistence data derived from [redacted]: • Persistence on cabotegravir of [redacted] and [redacted] at [redacted], respectively	[redacted] demonstrates [redacted] in persistence associated with [redacted] (a [redacted]. This confirms that the +20% improvement assumed for cabotegravir is conservative. A scenario analysis using [redacted] is explored. Additional real-world evidence (RWE) supports a persistence improvement associated with

Cabotegravir for preventing HIV-1 in adults and young people [ID6255]
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Parameter	Previous value	New value	Justification
		• Persistence on TDF/FTC of [redacted] and [redacted] at [redacted], respectively	cabotegravir and long-acting modalities (see comment 3 of evidence submitted on April 11th). Further evidence and rationale are provided in Section 0.
Efficacy data used in CEM	Using primary HPTN analysis: 91.88% reduction in the incidence of HIV-1 acquisitions vs. no PrEP for the cabotegravir group for men who have sex with men and transgender women, 92.72% for cisgender women	Using injection phase only efficacy data (no oral lead-in [OLI]): 95.45% reduction in incidence of HIV-1 acquisitions for the cabotegravir group for men who have sex with men and transgender women, and 97.46% for cisgender women	US real-world evidence has demonstrated that 97.8% of individuals receiving Cabotegravir for PrEP **do not** receive the optional oral lead-in (OLI) (1) The OLI is optional in the UK Summary of Product Characteristics (SmPC) (5, 6). Therefore, to align with clinical prescribing practices, an [redacted] has been performed using efficacy data from HPTN-083 and HPTN-084 trials injection phase only (no OLI). As a simplifying assumption, these data have been assumed to apply to 100% of the model population. ViiV do not believe that applying the [redacted] to the estimated 2.2% of individuals who may receive OLI in clinical practice will materially impact the ICER. Further evidence and rationale are provided in Section 4.
% people receiving oral lead-in	• 50%	• 0% to align with new efficacy data (simplifying assumption – see justification).	

Abbreviations: CAB, cabotegravir; CEM, cost-effectiveness model; HIV, human immunodeficiency virus; ITC, indirect treatment comparison; PrEP, pre-exposure prophylaxis; PYs, person years; RWE, real world evidence; SmPC, summary of product characteristics; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; TFV: tenofovir; UK, United Kingdom; US, United States of America.

For further details, Table 4 shows the impact of each individual change on the base-case results when comparing cabotegravir with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). Table 5 shows the impact when comparing cabotegravir with no pre-exposure prophylaxis (PrEP). Both tables present results based on the cabotegravir patient access scheme (PAS).

3. New evidence confirming 20% persistence improvement for cabotegravir vs. TDF/FTC is a conservative assumption

The [redacted] of anonymised patient level data (APLD) measured the persistence of cabotegravir and oral TDF/FTC in individuals [redacted] PrEP between [redacted] (7). [redacted].

Results showed that cabotegravir has [redacted] persistence [redacted] cabotegravir users [redacted] showed high [redacted] and [redacted] persistence compared with persistence among [redacted] at [redacted] and [redacted]. [redacted] cabotegravir therefore represented a persistence [redacted] at [redacted] and [redacted] at [redacted] (Figure 1).

Figure 1: Persistence of cabotegravir [redacted] in individuals [redacted]

[redacted]

Source: ViiV Healthcare, 2025 (7).
Abbreviations: PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

In addition to the data on [redacted], an assessment of the [redacted] persistence rate across the cohort within the database and receiving cabotegravir [redacted]

[redacted] has been assessed between [redacted] (7). Results confirm consistent and sustained persistence [redacted] across the [redacted]. For individuals commencing PrEP in [redacted], [redacted] of individuals were persistent at [redacted] with cabotegravir compared to [redacted] persistent at [redacted], a [redacted] with cabotegravir (Figure 2).

Figure 2: Percentage of individuals persistent at [redacted] with cabotegravir [redacted]

Source: ViiV Healthcare, 2025 (7).
Abbreviations: PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

4. Use of [redacted] to reflect real-world evidence (RWE) demonstrating limited use of cabotegravir oral lead-in (OLI) within clinical practice

The cabotegravir for PrEP OLI is optional and is expected to be used in a minority of people accessing PrEP, but may be used to assess tolerability prior to administration of cabotegravir injections or as bridging oral PrEP for individuals who will miss a planned dose with cabotegravir injection (5, 6, 8).

No safety events occurred during the OLI phase of the clinical trials HPTN-083 and HPTN-084 (9, 10). As such, the licenced indication for use outlines that the OLI prior to the initiation of cabotegravir injection is optional (8). This has been further supported by pharmacokinetic clinical trials (11). In new data from a RWE study conducted at a single-centre in the US from July 2022 to December 2023, among 270 individuals commencing cabotegravir for PrEP, 97.8% of the population initiated cabotegravir for PrEP directly with the injection (1), meaning the use of oral lead-in was extremely uncommon.

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The primary endpoint of HPTN-083 and HPTN-084 was the number of documented incident HIV acquisitions in the OLI phase plus the injection phase (12, 13). In the OLI phase, participants received daily cabotegravir tablets for up to 5 weeks, before transitioning to cabotegravir injections every 2 months after initiation. In addition, a secondary endpoint of HPTN-083 and HPTN-084 was the number of documented incident HIV acquisitions during the injection phase only.

The OLI phase was implemented purely as a safety precaution as cabotegravir was the first long-acting injectable investigated for PrEP, and there was a need to ensure its tolerability profile. The efficacy of cabotegravir tablets as a standalone strategy for PrEP has not been evaluated.

Trial results have demonstrated there is a risk of HIV acquisition during the OLI due to sub-optimal adherence to oral PrEP (10, 14-16). Therefore, in combination with the licence, real-word evidence, trial methods and trial outcomes, it is appropriate to consider cabotegravir efficacy using only the injection phase of the trials. Accordingly, to ensure the analyses reflect anticipated UK clinical practice, we have removed the OLI data from the ITC (CITE), thereby providing more relevant evidence to inform the Committee's decision making.

Lastly, following the primary analysis of HPTN-083 and HPTN-084 conducted in 2020, extended retrospective virologic testing was performed to better characterise the timing of HIV acquisitions. As a result, a number of acquisitions that had previously been characterised as incident on cabotegravir for PrEP were determined to be a baseline acquisition. These analyses were considered as post-hoc analysis. Using the post-hoc analysis data allows for the inclusion of more recent and updated information from the HPTN trials, ensuring it accurately reflects the incidence of HIV and excludes baseline HIV acquisitions (those that occurred before the initiation of cabotegravir).

Table 2 presents the re-assessment of the efficacy of cabotegravir for PrEP across both primary (OLI plus injection phases) and secondary (injection phase only) end-points, based on outcomes which were both published and unpublished.

Table 2: Re-assessment of the effectiveness of cabotegravir for PrEP

Set of analysis population	**HPTN-083**	**HPTN-084**
Primary blinded analyses (oral lead-in and injection phases)	**Landovitz et al, 2021 (5, 10)**	**Delany-Moretlwe et al, 2022 (5, 9)**
• Reduction in risk of incident acquisition relative to oral TDF/FTC	**66%**	**88%**
• Incident cases in Cabotegravir / Incident cases in oral TDF/FTC	13 / 39	4 / 36
Post-hoc blinded analyses (oral lead-in and injection phases)	**Marzinke et al, 2021 (5, 15)**	**Delany-Moretlwe et al, 2022 (5, 9)**
• Reduction in risk of incident acquisition relative to oral TDF/FTC	**69%**	**90%**

Set of analysis population	HPTN-083	HPTN-084
• Incident cases in Cabotegravir / Incident cases in oral TDF/FTC	12 / 39	3 /36
[redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]
• [redacted]	[redacted]	[redacted]

Abbreviations: CAB, cabotegravir; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; CSR, clinical study report.

4.1. Overview of HPTN trial-derived inputs used in the revised analysis

This analysis includes the post hoc analysis of the blinded study period. The revised estimates show [redacted] observed in the cabotegravir group.

4.1.1. HPTN-083

Oral lead-in and injection phases: After exclusion of the baseline HIV acquisition from the cabotegravir group, 51 incident HIV-1 acquisitions were reported for the modified intention to treat population over 6404 person-years (PYs) of follow-up. Twelve occurred in the cabotegravir group (incidence of 0.37 per 100 PYs) and 39 occurred in the TDF/FTC group (incidence of 1.22 per 100 PYs). One additional case in the cabotegravir group was also identified post-hoc as a baseline acquisition. All 39 acquisitions in the TDF/FTC group were incident acquisitions; none were reclassified on post-hoc testing. There was consequently a 69% reduction in the incidence of HIV-1 acquisitions during OLI plus injection phase for participants in the cabotegravir group relative to participants in the TDF/FTC group (hazard ratio: 0.31; 95% confidence interval [CI]: 0.16, 0.58) (5).

Injection phase only: In the analysis of incident HIV-1 acquisitions occurring in the injection phase only (no OLI), [redacted] acquisitions occurred in the cabotegravir group (incidence of [redacted] per 100 PYs) and [redacted] occurred in the TDF/FTC group (incidence of [redacted] per 100 PYs). As such, an [redacted] reduction in the incidence of HIV-1 acquisitions was observed for the cabotegravir group compared with the TDF/FTC group during the injection phase only (hazard ratio: [redacted] 95% CI: [redacted]).

4.1.2. HPTN-084

Oral lead-in and injection phases: After exclusion of the baseline HIV acquisition from the cabotegravir group, 39 incident HIV-1 acquisitions were reported for the modified intention to treat population over 3906 PYs of follow-up. Three occurred in the cabotegravir group (incidence of 0.15 per 100 PYs) and 36 occurred in the TDF/FTC group (incidence of 1.85 per 100 PYs). One additional case in the cabotegravir group was also identified post-hoc as a baseline acquisition. All 36 acquisitions in the TDF/FTC group were incident acquisitions; none were reclassified on post-hoc testing. There was consequently a 90% reduction in the incidence of HIV-1 acquisitions during OLI plus injection phases for participants in the cabotegravir group relative to participants in the TDF/FTC group (hazard ratio: 0.04 95% CI: 0.10, 0.27) (5).

Injection phase only: In the analysis to evaluate incident HIV-1 acquisitions occurring during the injection phase only, [redacted] acquisition was reported in the cabotegravir group (incidence of [redacted] per 100 PYs) and [redacted] reported in the TDF/FTC group (incidence of [redacted] per 100 PYs). As such, a [redacted] reduction in the incidence of HIV-1 acquisitions was observed for the cabotegravir group compared with the TDF/FTC group during the injection phase (hazard ratio: [redacted] 95% CI: [redacted]).

In summary the superior efficacy of cabotegravir vs daily TDF/FTC in reducing the risk of HIV-1 acquisition is [redacted] when [redacted], demonstrating an [redacted] efficacy [redacted].

Table 3 summarises the new data informing the ITC.

4.1.3. Summarising the new estimates used in the original base case (submitted in Document B) alongside the revised base case (submitted in this addendum)

Table 3: Summary of new hazard ratios (HR) estimates for HIV acquisition used in the revised base case

Injection phase only – post hoc analysis of blinded study period	HPTN-083		HPTN-084	
	CAB	TDF/FTC	CAB	TDF/FTC
Number of HIV acquisitions	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	

Abbreviations: CAB, cabotegravir; CI, confidence interval; HR, hazard ratio; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Results of the [redacted] and application in the cost-effectiveness analysis

The results of the [redacted] are shown below. The estimated efficacy of cabotegravir versus no PrEP is [redacted] for the cisgender women population (HPTN-084 trial) and [redacted] for the men who have sex with men and transgender women population (HPTN-083 trial).

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Indirect comparison % Effectiveness for the HPTN 083 and HPTN 084 trial populations

	Submitted ITC in Document B			[redacted] **for addendum**		
Parameter	% Effectiveness			% Effectiveness		
	Mean	**2.5% CrI**	**97.5% CrI**	**Mean**	**2.5% CrI**	**97.5% CrI**
Cabotegravir versus no PrEP (HPTN-083 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabotegravir versus no PrEP (HPTN-084 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CrI, credible interval; HPTN, HIV Prevention Trials Network.

As previously stated, in absence of UK data to inform the underlying risk of HIV acquisition for cisgender women, the HIV incidence for the no PrEP arm estimated from the ITC using HPTN 084 data [redacted] was used. This has been [redacted] which estimated the background HIV incidence in cisgender women at [redacted]

In the CEM, the observed adherence in the HPTN-083 and HPTN-084 trials is used to estimate the percentage effectiveness of oral TDF/FTC versus no PrEP using the meta-regression equation. The meta-regression parameters have changed marginally due to the sample used, such that the resulting percentage effectiveness of oral TDF/FTC versus no PrEP used in the cost-effectiveness model also changed marginally: [redacted] in the updated CEM versus [redacted] in the previously submitted CEM.

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5. Revised base case results

Table 4: Revised company deterministic base-case results cabotegravir vs. TDF/FTC (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER vs baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
Previous company base-case results submitted in October 2024 in response to draft guidance							
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Revised company base-case results reflecting changes made as part of the additional evidence submission							
TDF/FTC	[redacted]	[redacted]					
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Scenario using persistence data taken from the [redacted]							
TDF/FTC	[redacted]	[redacted]					
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Scenario assuming oral lead-in of 50%							
TDF/FTC	[redacted]	[redacted]					
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: Dom, dominant; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; Incr., incremental; ITC, indirect treatment comparison; PAS, patient access scheme; PYs, person-years; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

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Table 5: Revised company deterministic base-case results cabotegravir vs. no PrEP (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
Previous company base-case results submitted in October 2024 in response to draft guidance							
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Revised company base-case results reflecting changes made as part of the additional evidence submission							
No PrEP	[redacted]	[redacted]					
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Scenario using persistence data taken from the [redacted]							
No PrEP	[redacted]	[redacted]					
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]
Scenario assuming oral lead-in of 50%							
No PrEP	[redacted]	[redacted]					
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]	[redacted]

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; Incr., incremental; ITC, indirect treatment comparison; PAS, patient access scheme; PYs, person-years; QALY, quality-adjusted life year, TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

6. Conclusion

In conclusion, the additional evidence presented in this addendum shows that a 20% persistence advantage for cabotegravir over TDF/FTC is extremely conservative. Furthermore, the [redacted] shows an [redacted] efficacy [redacted] when the optional oral lead in is not observed, as shown in RWE and is often the case in clinical practice.

ViiV considers 3.9/100 PYs a reasonable and conservative assumption to inform the incidence rate for the men who have sex with men and transgender women cohort in the economic model. This is aligned with the additional evidence for the baseline risk of HIV acquisitions addressed in the April 11th 2025 submission. Following the [redacted], a baseline risk for the cisgender women cohort of [redacted] is now considered.

Considering the baseline risk and the additional evidence to inform cost-effectiveness of cabotegravir, the updated base case confirms previous analyses provided by ViiV which demonstrated the value of cabotegravir for people at high risk of HIV acquisition; in all scenarios presented cabotegravir is dominant compared to TDF/FTC and no PrEP.

Recent international funding cuts have drastically changed projections of global HIV acquisitions (17), and this will have an impact on the risk of acquiring HIV among people at high risk within the UK. Even before these recent aid policy changes, the UK was projected to miss the UK HIV Action Plan's target of zero new HIV transmissions by 2030 (2, 18). To protect the health of those who live in the UK and to eradicate new HIV transmissions by 2030, urgent and increased efforts are imperative.

ViiV appreciate the opportunity to submit further evidence, and hope that the commentary provided addresses some of the remaining points to help the Committee to make a positive recommendation on cabotegravir for the prevention of HIV-1 in people at high risk of HIV acquisition.

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Appendix A: Sensitivity analysis for revised base case

A1. Probabilistic sensitivity analysis

Table 6: PSA base-case cost-effectiveness results for cabotegravir vs. TDF/FTC (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
TDF/FTC	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	-£36,179	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine.

Table 7: PSA base-case cost-effectiveness results for cabotegravir vs. no PrEP (cabotegravir PAS price)

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER versus baseline (£/QALY)	Incr. NHB at £20,000 per QALY	Incr. NHB at £30,000 per QALY
No PrEP	[redacted]	[redacted]	–	–	–	–	–
Cabotegravir	[redacted]	[redacted]	[redacted]	[redacted]	-£58,618	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; Incr., incremental; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year.

Figure 3: Cost-effectiveness scatterplot of cabotegravir vs. TDF/FTC (cabotegravir PAS price)

Abbreviations: PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 4: Cost-effectiveness scatterplot of cabotegravir vs. no PrEP (cabotegravir PAS price)

Abbreviations: PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

Figure 5: Cost-effectiveness acceptability curve of cabotegravir vs. TDF/FTC (cabotegravir PAS price)

Abbreviations: PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; TDF/FTC, Tenofovir disoproxil fumarate with emtricitabine.

Figure 6: Cost-effectiveness acceptability curve of cabotegravir vs. no PrEP (cabotegravir PAS price)

Abbreviations: PAS, patient access scheme; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

A2. Deterministic sensitivity analysis

Figure 7: Tornado diagram with cabotegravir vs. TDF/FTC (cabotegravir PAS price)

Abbreviations: ARV, antiretroviral; cabotegravir LA, cabotegravir long-acting; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; PAS, patient access scheme; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TDF/FTC, tenofovir disoproxil fumarate with emtricitabine.

Figure 8: Tornado diagram with cabotegravir vs. no PrEP (cabotegravir PAS price)

Abbreviations: ARV, antiretroviral; CGW, cisgender women; CI, confidence interval; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; PAS, patient access scheme; PK, pharmacokinetic; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SMR, standardised mortality ratio; TGW, transgender women.

BHIVA welcomes the opportunity to provide further evidence on comment on this appraisal.

HIV acquisition risk

While it was not possible to observe the latest meeting, we understand that the figure considered for baseline HIV acquisition was the incidence in the people who did not use PrEP in the IMPACT study conducted in the NHS. If this is the case, it is hard to overemphasise how inappropriate this is.

A baseline HIV acquisition risk of 1 per 100 person years or lower is likely to be a significant under-estimate for those assessed as candidates for the use of cabotegravir PrEP. In those at higher risk and not on PrEP, it seems reasonable to assume a baseline acquisition risk of 2-3 per 100 person years as a minimum.

The aim of PrEP is to provide a prevention intervention to those judged to be at higher risk of HIV acquisition. In the general population of people attending sexual health services, there will be a very wide range of risk for HIV acquisition, given the broad range of services provided for different people. In the main IMPACT publication, the HIV incidence in gay, bisexual and other men who have sex with men (GBMSM) who did not use PrEP was 0.95 (95% CI 0.88-1.03) per 100 person-years[1]. It is important to remember that PrEP was not available as an NHS service at the time of the IMPACT study, so there was significant demand in people at risk. GBMSM who were not assessed as at higher risk of HIV in sexual health services, or who chose not to go into IMPACT, are therefore likely to be a very different population from those that would be assessed as suitable for cabotegravir PrEP. Importantly, the IMPACT trial protocol stated that the HIV incidence in GBMSM at higher risk of HIV (e.g. those with a history of an acute bacterial STI) was around 3 per 100 person years (identified from GUMCAD). The HIV incidence in those who used PrEP in IMPACT was 0.13 (95% CI 0.08-0.19) per 100 person years, suggesting a reduction in risk of HIV acquisition with PrEP, but IMPACT was not designed to address efficacy of PrEP in higher risk individuals.

Important context is provided by the incidence rates in randomised controlled trials of oral PrEP, used in people assessed as at higher risk of HIV. In general, in these studies the incidence of HIV in GBMSM prescribed PrEP is approximately 1 per 100 person-years or lower:

- PROUD[2] = 1.2/100 person-years
- IPERGAY[3] = 0.91 per 100 person-years
- DISCOVER[4] = 0.16 per 100 person-years in those on tenofovir alafenamide/emtricitabine (TAF/FTC) and 0.34 per 100 person-years in those on tenofovir-df/emtricitabine (TDF/FTC)
- HPTN 083[5] = 1.22 per 100 person-years in those on TDF/FTC

All the above studies in (mainly) GBMSM confirmed high efficacy. While cross comparison of different studies has important caveats, it is worth observing that in general, PrEP reduces the incidence of HIV in these trial populations to a figure comparable to the non-users of PrEP in IMPACT.

There are no trials of oral PrEP in cisgender women in the UK. The majority of these studies have been carried out in Africa and efficacy has been low because of low adherence to oral PrEP. The incidence of HIV in more recent RCTs using oral PrEP in women are as follows:

- HPTN 084[6] = 1.85 per 100 person years in women on TDF/FTC
- PURPOSE 1[7] = 1.69 per 100 person years in women on TDF/FTC; 2.02 per 100 person years in those on TAF/FTC; background HIV incidence = 2.41 per 100 person years

It may be difficult to extrapolate from studies conducted in Africa. However, in the UK, HIV diagnoses disproportionately affect heterosexual men and women of African origin, so it may be reasonable to assume similarities between this migrant population and populations in their country of origin.

Issues around the use and impact of Cabotegravir

Populations with unmet PrEP need

Clinical use of oral PrEP in the UK has mainly involved use in gay, bisexual and other men who have sex with men. As a group these individuals are at higher risk of HIV acquisition, but clinical risk assessment would also involve assessment of other recognised risk factors such as infectious syphilis, a rectal STI, or a history of chemsex. The recent UKHSA report shows that the historical decline in HIV diagnoses in GBMSM has not continued, with a levelling off indicating that there is unmet need in this group[8]. HIV testing in GBMSM now exceeds levels in 2019, but it is not clear to what extent this reflects repeat testing in the same individual vs any increase in people who have not tested before. Migrants who are less familiar with the healthcare system, racially minoritised GBMSM and others who face barriers to healthcare may be particularly well served by the offer of long acting, injectable PrEP.

The use of PrEP is also recommended in people likely to have similar risk as GBMSM. The proportion of PrEP users in the UK who are heterosexual is markedly smaller than the proportion of heterosexual people who are newly diagnosed with HIV in the UK. This is particularly true for women in whom diagnoses first made in England are rising[8]. There is no comment on incidence among people acquiring HIV through heterosexual sex in England. However, previous public health reports have estimated that just over half of diagnoses in this group are acquired in the UK[9]. The rising trend in diagnoses is of concern in this context. HIV testing among heterosexual people has recovered at a slower pace than GBMSM and transmission in the UK is continuing, but PrEP use remains low.

It is uncertain how an improved service offer with injectable PrEP will increase uptake among people who are at risk of HIV acquisition but not currently using PrEP. However, there is evidence in other settings that it may lead to improved outcomes, as described below.

The importance of choice of method

There are research studies that have shown that in people at higher risk of HIV, offering choice of PrEP intervention improves outcomes. For example, the SEARCH trial randomised participants to standard of care vs a dynamic choice intervention in the delivery of PrEP[10]. The extension to this study included the option to choose cabotegravir as PrEP. This study was conducted in heterosexual people in Uganda and Kenya and in the intervention group, the proportion of follow-up covered by PrEP was 69.7% vs 13.3% in the standard of care arm. 56% of participants chose cabotegravir and 53% chose oral PrEP.

Effects on persistence and who might benefit most from cabotegravir

Further implementation and observational studies of cabotegravir PrEP have been presented at the recent CROI conference in San Francisco. The ImPrEP study in Brazil recruited young GBMSM, transgender and non-binary people with no history of PrEP use, offering a choice of cabotegravir and oral PrEP[11]. Cabotegravir was chosen by 83% and adherence to injections was assessed as at least 90%. PrEP coverage as assessed by medication possession ratio was 95% for cabotegravir and 58% for oral PrEP (assuming minimum of 4 doses of oral TDF/FTC per week). Cabotegravir use in people attending Kaiser Permanente health systems in the USA was also reported at this conference[12]. In this report, 24% of those starting cabotegravir reported no previous PrEP use, despite oral PrEP having been freely available in the USA for some years. The cabotegravir users were more likely to Black / African American. 75% remained on cabotegravir at 12 months. In both studies, there were no participants on cabotegravir who acquired HIV.

In previously submitted evidence, we noted that in a sub-study of the HPTN 083 trial, HIV incidence was substantially higher in African American GBMSM taking TDF/FTC compared with other ethnic groups (2.11% vs 0.63%), despite reporting similar numbers of sexual partners[13]. The corresponding incidence in African American GBMSM randomised to cabotegravir was 0.58%. This was largely related to lower adherence to TDF/FTC in this group – as determined by drug levels – while attendance for on-time cabotegravir injections was high and similar between the two groups. It is likely that minoritised communities, in addition to people who are vulnerable owing to psychosocial difficulties, or who are particularly affected by stigma, will see more benefit from use of cabotegravir.

This evidence suggests that choice and the use of cabotegravir may increase the uptake of PrEP and that coverage is improved in comparison with oral PrEP. This may be particularly true in people who are less well served by current PrEP services and interventions, and who may have more difficulty in adhering to oral PrEP. These studies, as well as open label extensions of RCTs using injectable PrEP have shown that preference for each intervention is largely related to the formulation of drug [14 15]. Adherence to oral medication is particularly affected by the impact of stigma, with injectable PrEP offering a substantial benefit in facilitating discrete use.

Managed access

Clinicians can readily identify individuals who would benefit from injectable PrEP. Managed access would offer the opportunity to provide cabotegravir to these people while collecting important data to understand use in the English setting. A programme such as this could answer questions around whether the offer of injectable PrEP increases uptake and persistence among key populations and those less well served by the current oral PrEP offer. Data that

could be relatively easily collected would include demographics, past sexual health service and PrEP utilisation, adherence, coverage and discontinuation.

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National AIDS Trust Response to NICE consultation on cabotegravir for PrEP (ID6255)

The National AIDS Trust (NAT) welcomes the opportunity to respond to NICE's consultation on the appraisal of long-acting injectable cabotegravir (CAB-LA) for HIV pre-exposure prophylaxis (PrEP).

We strongly support NICE recommending CAB-LA, as it has the potential to play a vital role in preventing HIV transmission, reducing health inequalities, and helping the UK Government meet its target of ending new HIV cases by 2030.

We address below the specific evidence requests and discussion points raised in NICE's cover note of 14 March 2025.

Baseline risk of HIV acquisition

We recommend that the committee considers adopting a scenario-based approach to baseline HIV incidence, rather than a single point estimate. A single point estimate cannot adequately represent the diverse pathways to HIV risk. Behavioural and social determinants vary significantly, including unstable housing, substance use, stigma, and partner dynamics.

A range of baseline incidence scenarios would better capture the complexity and support a more accurate cost-effectiveness model. Modeling could include a range of incidence values to reflect different high-risk subpopulations (eg GBMSM, migrants, women, transgender people) and markers of higher risk including condomless sex and chem-sex. This will ensure that CAB-LA is evaluated against the populations who would actually receive it, rather than against an artificially broad group that includes lower-risk individuals.

The UKHSA's latest surveillance indicates that HIV transmission continues in groups with historically lower PrEP uptake. Notably, new diagnoses in England increased by 51% from 2022 to 2023, with the highest rises among heterosexual men and women.[1] Diagnoses in heterosexual women rose by ~30% (602 to 780 cases), and among heterosexual men by ~36% (445 to 605), with disproportionate impact on Black African communities (a 64% increase).[2]

While some of this increase is due to increased testing and people continuing their HIV care in England (53% of 2023 diagnoses were in people previously diagnosed abroad), the data confirm ongoing UK-acquired infections in groups underserved by current prevention efforts. These trends supports the evidence that particular communities (including minoritised ethnic groups, migrants, women with high-risk partners) have significant baseline HIV risks if not reached by PrEP. A one-size-fits-all baseline incidence (especially a low estimate) would fail to reflect these realities.

[1] https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2024-report#:~:text=,%28301%20to
[2] ibid

In addition, as previously raised to the committee, we shared concerns from BHIVA and other experts that it is inappropriate to consider baseline HIV acquisition from the incidence in the people who did not use PrEP in the IMPACT study conducted in the NHS.

We believe that the risk of acquiring HIV among individuals at substantial risk (and not on PrEP) in the UK is higher than the ~1 per 100 person-years figure derived from the IMPACT trial's non-PrEP group. Considering studies which have been shared to the committee, we believe a baseline incidence of 2–3 per 100 person-years (or higher in some subgroups) is more realistic for those who would be considered for CAB-LA.

Who might receive CAB-LA if it were available and how this affects the baseline risk of HIV acquisition

As previously shared with the Committee, CAB-LA is not intended to replace oral PrEP for those using it effectively. Instead, it is expected to better serve communities for whom daily oral PrEP is unsuitable, inaccessible, or unsustainable. This includes:

- Racially minoritised GBMSM
- Trans and non-binary communities who face substantial healthcare barriers
- Women from Black African and other high-prevalence communities, often underrepresented in PrEP access
- Migrants
- People who inject drugs and others with underserved needs that include people who are homeless and in unstable housing, and those experiencing intimate partner violence

Oral PrEP uptake among these groups has historically been low. Structural inequalities, stigma, and competing life priorities often make daily adherence unrealistic. For example, recent UKHSA data show that Black African communities experienced a 64% increase in new HIV diagnoses from 2022 to 2023, andexperienced a 30% increase - yet they remain underrepresented in oral PrEP programmes.

Real-world evidence from the ImPrEP Brazil study[3], the TRIO cohort in the US[4], and UK clinical feedback show strong preferences for injectable options in communities with historically poor adherence to oral PrEP. The majority of CAB-LA users in those studies were new to PrEP. The option of injectable PrEP improves both the reach and the quality of HIV prevention for these underserved groups.

Commissioning CAB-LA would directly support the UK Government's HIV Action Plan[5] and PrEP Roadmap[6] by expanding access to PrEP beyond traditional delivery models and reducing inequities in uptake.

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[3] https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(22)00331-9/fulltext
[4] https://www.gsk.com/en-gb/media/press-releases/viiv-healthcare-shows-more-than-99-effectiveness-in-real-world-studies-for-apretude/
[5] https://www.gov.uk/government/publications/towards-zero-the-hiv-action-plan-for-england-2022-to-2025
[6] https://www.gov.uk/government/publications/roadmap-for-meeting-the-prep-needs-of-those-at-significant-risk-of-hiv/roadmap-for-meeting-the-prep-needs-of-those-at-significant-risk-of-hiv

Commissioning CAB-LA would directly support the UK Government's HIV Action Plan and PrEP Roadmap by preventing new HIV transmissions, expanding access to PrEP beyond traditional delivery models and reducing inequities in uptake.

Economic modelling Issues

Recent findings highlight the potential of cabotegravir PrEP to improve uptake and adherence. The ImPrEP study in Brazil offered young GBMSM, trans, and non-binary people with no prior PrEP use a choice between cabotegravir and oral PrEP; 83% chose cabotegravir, with 90% injection adherence and 95% coverage, compared to 58% for oral PrEP.[7] In the US, data from Kaiser Permanente showed that 24% of those starting cabotegravir had never used PrEP before, despite free oral PrEP availability. Users were more likely to be Black/African American, and 73% remained on cabotegravir at 12 months.[8] No HIV acquisitions occurred among cabotegravir users in either study.

Previous evidence from HPTN 083 showed HIV incidence among African American GBMSM was higher with oral PrEP (2.11%) than with cabotegravir (0.58%), linked to lower oral PrEP adherence.[9] Injection attendance was consistently high. These findings suggest CAB-LA may better serve minoritised groups and those facing psychosocial or adherence barriers in the UK.

Overall, CAB-LA appears to improve PrEP uptake and coverage, particularly among those underserved by current services. Preference is often driven by formulation, with injectables offering a discrete alternative that may mitigate stigma-related adherence challenges. We believe assuming equivalent adherence across PrEP types underestimates the additional benefit of CAB-LA.

While some users may switch between oral and injectable PrEP, such transitions are expected to be limited. Most CAB-LA users will be individuals who cannot or will not use oral PrEP. Any transitions should be managed via clinical discretion and should not significantly impact modelling. Where switching does occur, data from the PILLAR study and others indicate retention and minimal discontinuation.[10]

As previously shared with the committee, we believe NICE's proposal to use a 10-year at-risk period for HIV acquisition in their economic model overestimates the likely duration of continuous PrEP use for most individuals. We believe the company's recommendation of a 5-year period is more aligned with real-world data and clinical practice. Given the dynamic nature of HIV risk, which can fluctuate due to changes in personal circumstances such as relationship status or behaviour, it is unlikely that most individuals will require PrEP for a full 10 years without interruption. In addition, the use of a 5-year period ensures a more accurate reflection of costs and benefits, avoiding the overestimation of both the time people remain at high risk and the costs associated with PrEP use over their lifetime. As clinical experts

[7] https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(22)00331-9/fulltext

[8] https://pmc.ncbi.nlm.nih.gov/articles/PMC11345832/

[9] https://www.nejm.org/doi/full/10.1056/NEJMoa2101016

[10] https://viivexchange.com/medical/nonl/is-cab-prep/pillar-study/

have indicated, five years captures a realistic at-risk period for many individuals, making it a more appropriate assumption for modelling HIV prevention strategies

We believe cost-effectiveness modelling should incorporate greater consideration of the communities with a higher baseline risk of HIV acquisition that are more likely to use CAB-LA in practice, the improved persistence and adherence among CAB-LA users and real-world usage scenarios based on behavioural and structural factors.

The potential for managed access for cabotegravir

NAT recognises the value of managed access programmes in health technology assessment processes but, in this instance, strongly believes that the evidence base supports full recommendation of CAB-LA use in routine practice, rather than limiting access through a managed access arrangement.

We believe the evidence base is robust enough to justify this recommendation without restricting access through a managed access programme. Following the Scottish Medicines Consortium recommendation of CAB-LA for use in Scotland, we believe the medicine should urgently be recommended as an effective and needed HIV prevention option. Introducing further delays and additional barriers to access would delay crucial interventions for groups currently underserved by oral PrEP and undermine the UK's ambition to end new HIV transmissions by 2030.

We appreciate that NICE may still seek real-world data on persistence, transitions, and cost assumptions. However, these are common implementation uncertainties, and should not preclude a positive recommendation. We believe such evidence could continue to be collected through routine commissioning and existing national surveillance mechanisms.

However if a full recommendation of CAB-LA for routine practice was not possible at this stage, we believe a managed access programme would be beneficial and preferable to not being recommended. In the short-term, managed access could provide cabotegravir to key populations while gathering valuable data on its use in England and Wales. Adding to the further evidence shared our submission, it would help further assess whether injectable PrEP improves uptake and persistence, especially among those underserved by oral PrEP. Key data collected could include demographics, past service use, adherence, coverage, and discontinuation.

Trends in HIV incidence in England

Key points

- There is evidence of a marked decline in HIV incidence in gay, bisexual and other men who have sex with men (GBMSM) between 2014/15 to 2022/23
- While no formal incidence estimates for people exposed to HIV through sex between men and women exist, the rise in HIV diagnoses in this group between 2021 and 2023 together with sustained HIV test positivity and lower levels of HIV testing in sexual health services suggest HIV transmission is not declining
- Since 2014, there has been a scale up of HIV combination prevention including HIV pre-exposure prophylaxis, HIV testing, and rapid initiation of treatment after an HIV diagnosis

Baseline risk of HIV acquisition in GBMSM

Background

Estimates of HIV incidence rates among all gay, bisexual, and other men who have sex with men (GBMSM) attending sexual health services (SHS) have previously been derived using national surveillance data, with findings published for 2012 (1) and 2014 (2,3). These analyses also derived incidence rates amongst population subgroups with HIV clinical risk markers relating to HIV testing and bacterial STI diagnosis history (1–3). We replicated this analysis using current surveillance data to derive annual HIV incidence rates among GBMSM from 2014 to 2023 with further stratification by HIV pre-exposure prophylaxis (PrEP) use.

Since 2014 there have been a number of changes in the HIV prevention landscape which may have influenced HIV incidence rates: the introduction of HIV PrEP to reduce risk of HIV infection; more widespread HIV testing and more frequent testing of people at higher risk of HIV to detect new HIV diagnoses; and increased coverage of antiretroviral therapy including more rapid initiation of treatment after an HIV diagnosis to reduce the risk of HIV transmission (4,5)[1].

Methods

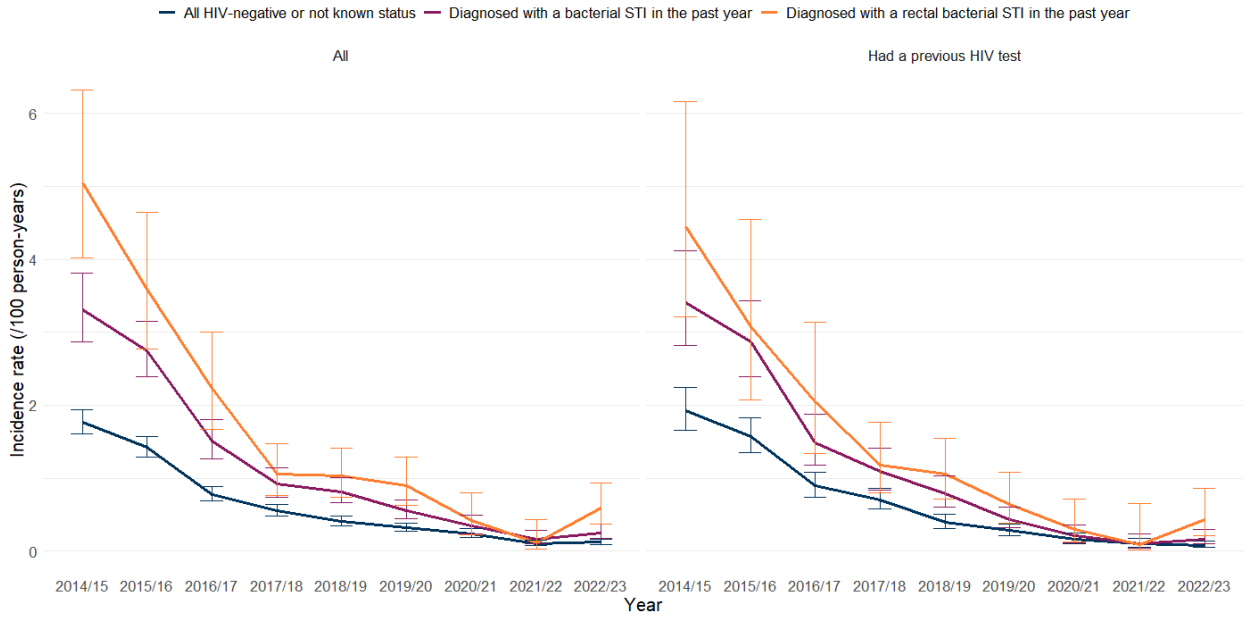
The analysis uses data from GUMCAD, the national STI surveillance system in England that collects data of all attendances, HIV tests, and HIV and STI diagnoses at SHS in England. Kaplan-Meier analysis was used to estimate annual HIV incidence rates per 100 person-years (py) amongst GBMSM attending SHS between 2014 and 2023. Individuals are followed up from their first HIV test in the year of interest until their last attendance or until they were newly diagnosed with HIV within 365 days of their first HIV test in that year. This analysis therefore restricts the study population to GBMSM with at least two HIV tests within the follow-up period.

[1] Prior to 2015, NHS clinical commissioning policy was to initiate antiretroviral therapy only when an HIV positive individual had already sustained a level of damage to the immune system, measured by a CD4 count of <350 cells/mm^3 (6).

Results

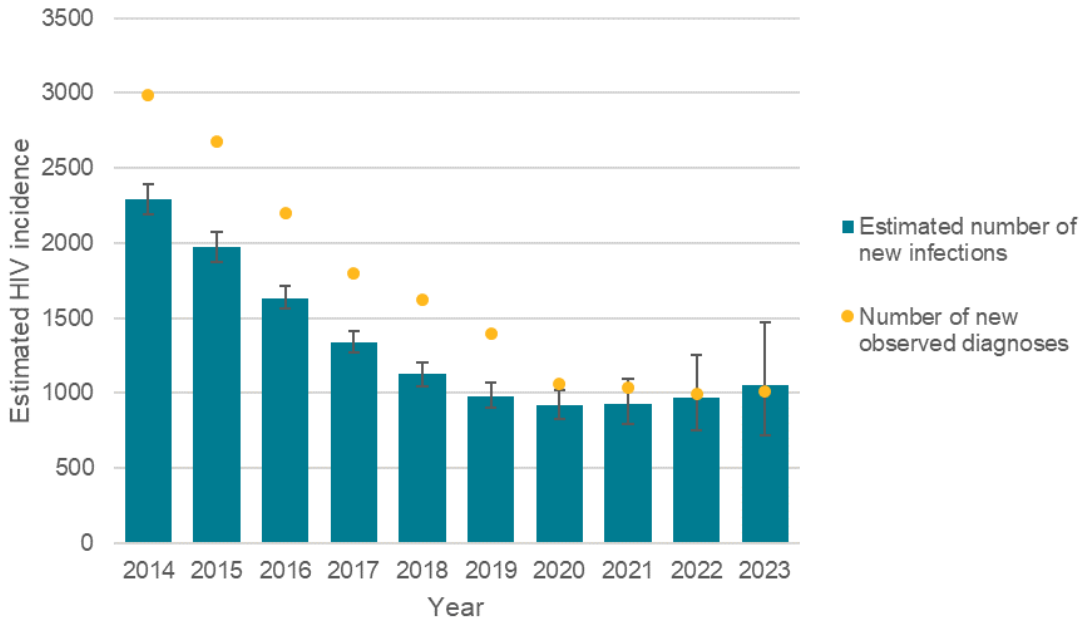
HIV incidence rates have declined across all GBMSM subgroups between 2014/15 and 2022/23 (Figure 1). In 2014/15, the subgroup with the highest HIV incidence rate was those with a recent rectal bacterial STI, followed by those with a history of a recent rectal bacterial STI diagnosis and negative HIV test; HIV incidence per 100-person years was 4.9 [95% CI 3.9 – 6.2] amongst those with a rectal bacterial STI in the previous year, and 3.9 [95% CI 2.8 – 5.6] amongst those with both a rectal bacterial STI diagnosis and a HIV test in the previous year (Appendix: Table 1) (3). In 2022/23, HIV incidence remained highest in these two subgroups of GBMSM (0.59 [95%CI 0.37-0.94] amongst those with a rectal bacterial STI in the previous year, and 0.43 [95%CI 0.22-0.87] amongst those with a rectal bacterial STI diagnosis and a HIV test in the previous year). The same patterns are also observed when stratifying HIV incidence by PrEP status (Appendix: Table 2).

Figure 1: Annual HIV incidence rates among GBMSM attending sexual health services (SHS) in England, 2014/15-2022/23



UKHSA also publishes estimates of new infections amongst all GBMSM, using a CD4 back-calculation method and new observed diagnoses amongst GBMSM in all settings reported in the HIV and AIDS New Diagnoses and Deaths Database (HANDD). These estimates are reported in the HIV Monitoring and Evaluation Framework (7), and extended below to include estimates from 2014. They show a similar trend of markedly decreasing incidence (using the CD4 back-calculation method) and new diagnoses of HIV between 2014 and 2020 (Figure 2).

Figure 2: estimated number of new infections using a CD4 back-calculation method, and new observed diagnoses in GBMSM, England, 2014 to 2023



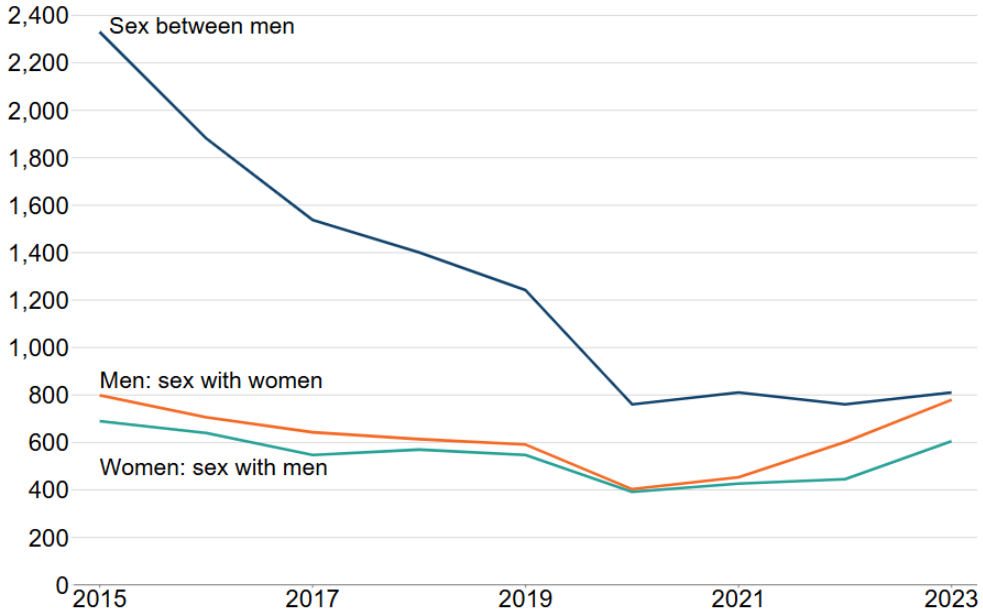
These analyses provide the results of multiple methods to monitor HIV incidence until the end of 2023, and all provide evidence of a decrease in incidence. A slight rise was observed in HIV incidence rates in 2022/23, compared to 2021/22, although the confidence intervals for these estimates overlap and this trend is not statistically significantly different.

Baseline risk of HIV acquisition in women

There is less current evidence for HIV incidence in women in England, including women at high risk of HIV. The first incidence estimates for heterosexuals in England were published in 2018, using a recent infection testing algorithm to identify recently acquired HIV amongst heterosexuals attending sexual health services between 2009 and 2013 (8). Amongst all heterosexuals, incidence rates per 100 person-years were estimated to be between 0.03 (95% CI 0.02-0.05) and 0.05 (95% CI 0.03-0.07) over the period. Incidence per 100 person years amongst black African heterosexuals was 4-5-fold higher, and increased slightly (although non-significantly) from 0.15 (95% CI 0.05-0.26) in 2009 to 0.19 (95% CI 0.04-0.34) in 2013.

UKHSA monitors trends in HIV diagnoses, specifically HIV diagnoses first made in England, together with trends in HIV test positivity as proxies for new transmission (9). The figure below from UKHSA's HIV Monitoring and Evaluation Framework shows that total new HIV diagnoses first made in England amongst all women likely exposed through sex with men have remained relatively stable since 2015, with a gradual decrease from 2015 to 2020 and a slight increase between 2021 and 2023 (Figure 3). While no formal incidence estimates for people exposed through sex between men and women exist, the rise in HIV diagnoses in this group together with sustained test positivity and lower levels of HIV testing in sexual health services suggest HIV transmission is not declining (7).

Figure 3: New HIV diagnoses by gender identity and probable route of exposure, England 2015 to 2023



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Appendix

Table 1: HIV incidence rates among GBMSM attending SHS who were repeat HIV testers, by clinical markers of HIV risk, in 2014/15, and in 2022/23

Clinical markers of risk	**2014/15**		**2022/23**	
	Repeat testers	**Rates per 100 py (95%CI)**	**Repeat testers**	**Rates per 100 py (95%CI)**
HIV negative or unknown (Total)	37,576	1.77 (1.61-1.94)	56,900	0.11 (0.08-0.15)
[a] Bacterial STI diagnoses in the previous year	8,704	3.31 (2.87-3.81)	15,326	0.16 (0.10-0.28)
[b] Recent rectal bacterial STI in the previous year (subset of [a])	2,313	5.04 (4.02-6.32)	4,179	0.11 (0.03-0.43)
[c] history of HIV test in the previous 42-365 days including [a] and [b] within this group	12,921	1.93 (1.66-2.24)	24,123	0.10 (0.06-0.17)
Subset of [c] with bacterial STI diagnoses in the previous year	4,553	3.40 (2.81-4.12)	9,625	0.10 (0.04-0.23)
Subset of [c] with rectal bacterial STI in the previous year	1,203	4.44 (3.21-6.16)	2,430	0.09 (0.01-0.65)

Table 2: HIV incidence rates among GBMSM attending SHS who were repeat testers, by clinical markers of risk and PrEP use, in 2022/23

Clinical markers of risk	**Repeat testers**	**HIV risk reduction among PrEP users**	**Not On PrEP**	**Using PrEP**
			Rates per 100 py (95%CI)	**Rates per 100 py (95%CI)**
HIV negative or unknown (Total)	56,900	-86%	0.36 (0.26-0.50)	0.05 (0.03-0.08)
[a] Bacterial STI diagnoses in the previous year	15,326	-91%	0.94 (0.62-1.45)	0.08 (0.04-0.17)
[b] Recent rectal bacterial STI in the previous year (subset of [a])	4,179	-91%	1.90 (1.13-3.21)	0.17 (0.06-0.46)
[c] history of HIV test in the previous 42-365 days including [a] and [b] within this group	24,123	-87%	0.31 (0.15-0.61)	0.04 (0.02-0.09)
Subset of [c] with bacterial STI diagnoses in the previous year	9,625	-89%	0.75 (0.36-1.58)	0.08 (0.03-0.19)
Subset of [c] with rectal bacterial STI in the previous year	2,430	-79%	1.22 (0.46-3.25)	0.26 (0.10-0.70)

SUBJECT: Single Technology Appraisal Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

From: Dr Rachael Jones, Consultant Physician HIV/GUM, NHSE HIV CRG and Chelsea and Westminster Hospital NHS Foundation Trust

Date: 11.04.2025

Dear NICE TA Team,

Re: Single Technology Appraisal Cabotegravir for preventing HIV-1 in adults and young people [ID6255]

Many thanks for the opportunity to provide a further response to the Cabotegravir (CAB) HIV PrEP appraisal. For clarity, I have addressed the on-going uncertainties highlighted in turn.

In addition, for completeness, we welcome any further comments or points that stakeholders may wish to raise on other uncertainties explored by the committee; in particular:

Who might have cabotegravir in practice if it were made available, and how this affects the baseline risk of HIV acquisition

As expressed at the second meeting, I have major concerns with using the IMPACT trial as an indicator of HIV prevalence and feel very disappointed that such weight has been ascribed to its findings. I feel this is a major flaw within the appraisal which undermines any valid outcome.

HIV pre-exposure prophylaxis and its implementation in the PrEP Impact Trial in England: a pragmatic health technology assessment - The Lancet HIV

IMPACT was an implementation study, which was necessary in order to demonstrate that PrEP could be delivered within sexual health clinics. It was helpful in providing further information regarding the demand for PrEP, the unmet need and duration that an individual may require PrEP, however, it was not designed to inform incidence data.

IMPACT was a single arm, unblinded study which used a non-trial population attending sexual health clinics to provide a comparison group. This non-trial population would have been comprised of individuals with very low sexual health risk (as evidenced by the fact that they were not offered PrEP) which was likely to include asymptomatic individuals (there were no online services into which such individuals could be channel shifted at this time), those presenting for contraception, vaccines or non-sexual health needs e.g. genital skin conditions.

Overall, 49% of the non-trial population had no markers of high-risk and were thus ineligible for PrEP.

The low risk nature of the non-trial population is further demonstrated by the reduced incidence of STI rates overall. During follow-up, 80% of non-trial participants had NO STIs diagnosed- table 3 within the paper outlines these figures in more detail.

A better marker of HIV incidence in the UK would be the PROUD study.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00056-2/fulltext

At the time of conducting PROUD, the overall HIV incidence in England was 1.34/100 person years. PROUD was an open-label randomised trial performed within 13 sexual health clinics in England. The study team enrolled HIV-negative gay and bisexual men who have sex with men (GBMSM) who had had anal intercourse without a condom in the previous 90 days. Unlike IMPACT, participants were randomly assigned (1:1) to receive daily combined tenofovir disoproxil fumarate (245 mg) and emtricitabine (200 mg) either immediately or after a deferral period of 1 year. Randomisation was performed via web-based access to a central computer-generated list with variable block sizes (stratified by clinical site).

In the PROUD deferred arm, HIV incidence was 9/100 person years. I believe this, with the 3.9/100 person year figure used in the current BHIVA/BASHH HIV guidelines derived from GUMCAD data, to be better markers of HIV incidence in vulnerable individuals.

Focussing on women specifically, given the lack of useful data from the UK, it may be prudent to use incidence data from other large studies e.g. PURPOSE whose cohorts reflect those at HIV risk in England currently.

https://www.nejm.org/doi/full/10.1056/NEJMoa2407001

Background HIV incidence in the screened population (8094 participants) was 2.41 per 100 person-years (95% CI, 1.82 to 3.19).

As detailed in previous submissions, despite the roll out of oral PrEP, recent UKHSA data have demonstrated an increase in new HIV diagnoses in England (51% increase compared to 2022 for all diagnoses and 15% increase for those first diagnosed in England). European data show similar trends. The rise has disproportionately affected ethnic minority groups, leading to UKHSA to state that 'further provision of services is needed that are accessible to diverse key populations and culturally competent'.

https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2024-report

To me, in combination with the data illustrating the failure of oral therapies in recent PrEP studies, this demonstrates that our current PrEP options are not addressing the holistic needs of vulnerable cohorts, further evidenced by the fact that 50% of individuals newly diagnosed with HIV within the Dean Street cohort, one of the largest sexual health services in Europe, had used PrEP within three months of diagnosis (personal communication Jones/Whitlock, 2025).

As per previous submissions, I am concerned that the outcome of not recommending cabotegravir may represent health inequity and deny access to those most in need, thus leaving them at risk of HIV acquisition and hence I would argue that the provisional recommendations for CAB PrEP are not a sound and suitable basis for guidance to the NHS.

The current recommendation is also at risk of not promoting equality of opportunity or the elimination of discrimination and fails to foster good relations between people with particular protected characteristics as it will deny access to cohorts of individuals in whom current PrEP options are not appropriate in whom cabotegravir has been proven to be superior e.g. cis-women.

Current UKHSA data also show that the majority of PrEP users continue to be GBMSM. PrEP uptake in other at-risk cohorts remains low and PrEP inequity has increased with negative outcomes for some groups, particularly Black women as discussed in previous meetings and above. The HPTN data

serve to demonstrate the success of cabotegravir in all groups with much of the failure of oral therapy being linked to poor adherence. This has been seen in more recent studies of the injectable PrEP agent lenacapavir vs oral therapy.

https://www.nejm.org/doi/full/10.1056/NEJMoa2407001

As detailed in my previous submission, alternative PrEP options serve to improve PrEP access and uptake and provide an alternative for individuals in whom standard of care PrEP is not appropriate or inferior.

Since the initial rounds of evidence collection, multiple studies have been published to demonstrate that long acting injectable PrEP would increase PrEP uptake and persistence in those who have been 'left behind' by current PrEP agents and studies e.g.cis-women, people who inject drugs, those who struggle with adherence, oral meds or those in whom the current standard of care agents are contraindicated.

Preferential Initiation of Long-Acting Injectable Versus Oral HIV Pre-Exposure Prophylaxis Among Women Who Inject Drugs.
Roth AM, Bartholomew TS, Ward KM, Groves A, Mazzella S, Bellamy S, Amico KR, Carrico AW, Ironson G, Krakower D.
Clin Infect Dis. 2024 Sep 30:ciae450. doi: 10.1093/cid/ciae450. Online ahead of print.
PMID: 39347705

Health impact, budget impact, and price threshold for cost-effectiveness of lenacapavir for HIV pre-exposure prophylaxis in eastern and southern Africa: a modelling analysis.
Wu L, Kaftan D, Wittenauer R, Arrouzet C, Patel N, Saravis AL, Pfau B, Mudimu E, Bershteyn A, Sharma M.
Lancet HIV. 2024 Sep 20:S2352-3018(24)00239-X. doi: 10.1016/S2352-3018(24)00239-X. Online ahead of print.
PMID: 39312933

Provider Factors Likely to Impact Access and Uptake of Long-Acting Injectable Cabotegravir for Transgender Women in the United States: Results of a Qualitative Study.
Rael CT, Das D, Porter J, Lopez-Ríos J, Abascal E, Dolezal C, Vaughn MP, Giffenig P, Lopez JM, Stonbraker S, Sun C, Velasco RA, Bitterfeld L, Bockting WO, Bauermeister J.
J Assoc Nurses AIDS Care. 2024 Sep-Oct 01;35(5):437-449. doi: 10.1097/JNC.0000000000000488. Epub 2024 Aug 13.
PMID: 39137316

Weighing the Options: Which PrEP (Pre-exposure Prophylaxis) Modality Attributes Influence Choice for Young Gay and Bisexual Men in the United States?
Hill-Rorie J, Biello KB, Quint M, Johnson B, Elopre L, Johnson K, Lillis R, Burgan K, Krakower D, Whiteside Y, Mayer KH.
AIDS Behav. 2024 Sep;28(9):2970-2978. doi: 10.1007/s10461-024-04384-1. Epub 2024 Aug 10.
PMID: 39126557

. Perceptions of the attributes of new long-acting HIV pre-exposure prophylaxis formulations compared with a daily, oral dose among South African young women: a qualitative study.
Shamu P, Mullick S, Christofides NJ.
AIDS Care. 2024 Aug 6:1-11. doi: 10.1080/09540121.2024.2383878. Online ahead of print.
PMID: 39106972

Understanding Preferences for Visualized New and Future HIV Prevention Products Among Gay, Bisexual and Other Men Who Have Sex with Men in the Southern United States: A Mixed-Methods Study.

Denson DJ, Stanley A, Randall L, Tesfaye CL, Glusberg D, Cardo J, King AR, Gale B, Betley V, Schoua-Glusberg A, Frew PM.
J Homosex. 2024 Jul 11:1-19. doi: 10.1080/00918369.2024.2373803. Online ahead of print.
PMID: 38989968

The Global Impact of Diversifying PrEP Options: Results of an International Discrete Choice Experiment of Existing and Potential PrEP Strategies with Gay and Bisexual Men and Physicians.
Tagliaferri Rael C, Giguere R, Bryndza Tfaily E, Sutton S, Horn E, Schieffer RJ, Hendrix C, D'Aquila RT, Hope TJ.
AIDS Res Hum Retroviruses. 2024 May 28. doi: 10.1089/AID.2023.0120. Online ahead of print.
PMID: 38753738

Intention and preference to use long-acting injectable PrEP among MSM in the Netherlands: a diffusion of innovation approach.
Wang H, Zimmermann HML, van de Vijver D, Jonas KJ.
AIDS Care. 2024 Jul;36(sup1):89-100. doi: 10.1080/09540121.2024.2307378. Epub 2024 May 7.
PMID: 38713631

Willingness and preferences for long-acting injectable PrEP among US men who have sex with men: a discrete choice experiment.
Cole SW, Glick JL, Campoamor NB, Sanchez TH, Sarkar S, Vannappagari V, Rinehart A, Rawlings K, Sullivan PS, Bridges JFP.
BMJ Open. 2024 Apr 22;14(4):e083837. doi: 10.1136/bmjopen-2023-083837.
PMID: 38653510

Assessing Preferences for Long-Acting Injectable Pre-Exposure Prophylaxis Among Young Adult Sexual Minority Men and Transgender Women.
Weeden T, Garofalo R, Johnson AK, Schnall R, Cervantes M, Scherr T, Kuhns LM.
Acad Pediatr. 2024 Sep-Oct;24(7):1110-1115. doi: 10.1016/j.acap.2024.04.005. Epub 2024 Apr 15.
PMID: 38631476
Clinical Trial.

Perspectives on long-acting formulations of pre-exposure prophylaxis (PrEP) among men who have sex with men who are non-adherent to daily oral PrEP in the United States.
Rogers BG, Chan PA, Sutten-Coats C, Zanowick-Marr A, Patel RR, Mena L, Goedel WC, Chu C, Silva E, Galipeau D, Arnold T, Gomillia C, Curoe K, Villalobos J, Underwood A, Sosnowy C, Nunn AS.
BMC Public Health. 2023 Aug 28;23(1):1643. doi: 10.1186/s12889-023-16382-4.
PMID: 37641018

Who prefers what? Correlates of preferences for next-generation HIV prevention products among a national U.S. sample of young men who have sex with men.
Biello KB, Valente PK, da Silva DT, Lin W, Drab R, Hightow-Weidman L, Mayer KH, Bauermeister JA; iTech Team.
J Int AIDS Soc. 2023 Jul;26 Suppl 2(Suppl 2):e26096. doi: 10.1002/jia2.26096.
PMID: 37439061

Systematic review of the values and preferences regarding the use of injectable pre-exposure prophylaxis to prevent HIV acquisition.
Lorenzetti L, Dinh N, van der Straten A, Fonner V, Ridgeway K, Rodolph M, Schaefer R, Schmidt HA, Baggaley R.
J Int AIDS Soc. 2023 Jul;26 Suppl 2(Suppl 2):e26107. doi: 10.1002/jia2.26107.
PMID: 37439057

Systematic review of the values and preferences regarding the use of injectable pre-exposure prophylaxis to prevent HIV acquisition.
Lorenzetti L, Dinh N, van der Straten A, Fonner V, Ridgeway K, Rodolph M, Schaefer R, Schmidt HA, Baggaley R.
J Int AIDS Soc. 2023 Jul;26 Suppl 2(Suppl 2):e26107. doi: 10.1002/jia2.26107.
PMID: 37439057

Barriers and facilitators to HIV pre-exposure prophylaxis for cisgender and transgender women in the UK.
Whelan I, Strachan S, Apea V, Orkin C, Paparini S.
Lancet HIV. 2023 Jul;10(7):e472-e481. doi: 10.1016/S2352-3018(23)00080-2. Epub 2023 Jun 1.
PMID: 37271160

Exploring preferences and decision-making about long-acting injectable HIV pre-exposure prophylaxis (PrEP) among young sexual minority men 17-24 years old.
John SA, Zapata JP, Dang M, Pleuhs B, O'Neil A, Hirshfield S, Walsh JL, Petroll AE, Quinn KG.
Sci Rep. 2023 Mar 29;13(1):5116. doi: 10.1038/s41598-023-32014-8.
PMID: 36991027

Willingness to use and preferences for long-acting injectable PrEP among sexual and gender minority populations in the southern United States, 2021-2022: cross-sectional study.
Schoenberg P, Edwards OW, Merrill L, Martinez CA, Stephenson R, Sullivan PS, Jones J.
J Int AIDS Soc. 2023 Mar;26(3):e26077. doi: 10.1002/jia2.26077.
PMID: 36951057

Brief Report: Refusal of Daily Oral PrEP: Implementation Considerations and Reported Likelihood of Using Various HIV Prophylaxis Products in a Diverse Sample of MSM.
Mansergh G, Kota KK, Carnes N, Gelaude D.
J Acquir Immune Defic Syndr. 2023 Mar 1;92(3):212-216. doi: 10.1097/QAI.0000000000003134.
PMID: 36442153

Other economic modelling issues, including the impact of cabotegravir on persistence, the duration of the risk period that should be modelled, and the modelling of transitions from cabotegravir to oral PrEP

The recent Conference on Retroviruses and Opportunistic Infection (San Francisco, March 2025) has provided useful data in support of CAB which address the further uncertainties highlighted by the TA.

Long-acting Cabotegravir PrEP Uptake and Persistence in a Large U.S. Healthcare System

23 311 PrEP users, 180 (0.8%) using CAB PrEP
24% had never had oral PrEP

Those opting for CAB were more likely to be:
Older
Black/Hispanic
With higher rates of STIs/co-morbidities

CAB PrEP persistence rates 88% at 6/12, 75% at 12/12

Of those stopping 14/35 switched to oral PrEP

HIV incidence 0 in CAB arm.

ImPrEP CAB Brasil: Enhancing PrEP Coverage with CAB-LA in Young Key Populations

Implementation study in young GBMSM, non-binary, trans populations included. It is important to note that of those enrolled, 1200 (83%) chose CAB-LA of whom, 60% identified as non-white.

HIV incidence at one year was 0 in CAB LA arm, 1.5 in the comparison cohort of oral PrEP users.

PILLAR Month 12 Clinical Results: Zero HIV Acquisition and High Persistence With CAB LA for PrEP -

Enrolled 201 individuals
60% identified as Black or Latino
Trans-gender Men 6%

22% had not received oral PrEP in the previous 6/12

10% had an STI – on-going risk behaviour

HIV acquisition 0 in CAB arm.

These recent publications address some of the concerns which have been discussed in previous meetings e.g. 'opening the CAB PrEP flood-gates'. As demonstrated, CAB PrEP uptake has been low (<1%) in the 23 311 US PrEP users in the US Healthcare system outlined above.

Persistence rates were excellent within this study, with 75% of CAB users still on this agent at one year.

Where required, switches to oral PrEP were undertaken.

The potential for managed access for cabotegravir (including what evidence could be collected, how, and how that would address relevant uncertainties)

If possible, I would prefer to avoid a managed access pathway. There are already barriers to non-standard of care PrEP access in the UK, with all individuals requiring discussion within a dedicated complex PrEP multidisciplinary meeting and registration on the Bluteq system.

Furthermore, managed access has never been deployed within sexual health services, which are commissioned by local authorities as opposed to the NHS which may further complicate matters and cause unnecessary delay.

Kind regards,
Rachael Jones

External Assessment Group critique of stakeholder comments

Title: *Cabotegravir for preventing HIV-1 in adults and young people [ID6255]*

Produced by	Birmingham Centre for Evidence and Implementation Science
Date completed	08/05/2025

Please note that: Sections highlighted in [redacted].

Table of Contents

1 Introduction

Following the second Appraisal Committee meeting for cabotegravir (CAB-LA) for preventing HIV-1 in adults and young people, NICE requested additional evidence from all stakeholders. The main emphasis was on additional evidence of baseline risk of HIV acquisition, which has been addressed by the Decision Support Unit (DSU). The Birmingham Centre for Evidence and Implementation Science (BCEIS) has been asked to complete a narrative review of comments received from stakeholders on other issues/uncertainties in the appraisal, including:

- Who might have CAB-LA in practice if it were made available, and how this affects the baseline risk of HIV acquisition,
- Other economic modelling issues, including the impact of CAB-LA on persistence, the duration of the risk period that should be modelled, and the modelling of transitions from CAB-LA to oral PrEP,
- The potential for managed access for CAB-LA (including what evidence could be collected, how, and how that would address relevant uncertainties),
- Commercial arrangements (company only), and how CAB-LA may be commissioned and used in practice.

Evidence provided by stakeholders on these and other issues is discussed in turn. The EAG has not conducted a systematic review of evidence on these issues, nor has the company or other stakeholders. The review of evidence was undertaken by a single EAG reviewer with minimal checking due to time constraints. Clinical expert advice was sought by the EAG but could not be obtained.

2 Who might have cabotegravir in practice if it were made available, and how this affects the baseline risk of HIV acquisition

Three stakeholders (BHVA, National AIDS Trust, and Rachel Jones, consultant physician) provided evidence citations supporting their statements in response to the question of who might have CAB-LA in practice if it were made available, and how this affects the baseline risk of HIV acquisition. Thirty-one citations were provided in statements discussing the stakeholder's collective view that CAB-LA may improve

uptake of PrEP in situations where daily oral PrEP is inaccessible or unsuitable or for those who have difficulty with adherence to oral PrEP, and the stakeholders provided some examples of the types of communities this may be true for (stakeholder comments not summarised here). However, 12 references[1-12] do not offer evidence in direct support of the comments regarding who might have CAB-LA if made available and are not discussed further.

Of the remaining 19 studies, six received commercial funding, nine were non-commercially funded and four reported no funding or the funder was not reported. Eight were abstracts (one was a full paper but the EAG was not able to source the full publication)[13] and one was a systematic review.[14] All but two of the studies[15, 16] did not include UK or European participants, and the EAG considers the generalisability of the majority of studies to be low. Twelve studies were qualitative studies, preference studies or discrete choice methods studies looking at hypothetical sets of questions around various different choices of PrEP in a range of different populations,[13, 15-25] and while some of these provide limited support for the stakeholder's statements, owing to resource constraints these are not summarised further to allow focus on studies reporting real choices of PrEP.

Both the BHIVA and the National AIDS Trust cite data from the ImPrEP CAB study, which was supported by the company. A population of young gay, bisexual MSM, non-binary and transgender individuals within public health PrEP services in Brazil who were seeking PrEP or HIV testing were given choices between CAB-LA and oral PrEP. All participants were aged 18-30 years and all were PrEP naïve. The EAG concurs that the conference abstract reports that majority, 83%, chose CAB-LA.[26] This was, however, a selected group and may not offer any information about who might have CAB-LA in practice. There are also no details of how the choices were presented to these individuals in this conference abstract and the representativeness of this population to the NHS is likely low. The full publication that was cited doesn't appear to report these data.[2] Both stakeholders also cite evidence that among users of the Kaiser Permanente health systems in the USA, 24% of those starting CAB-LA had never used PrEP before, despite free oral PrEP availability. One of the cited references doesn't appear to report these data.[27] The other reference is an abstract only,[28] which states among 141 CAB-LA users enrolled in a health plan, 21.3% had no prior oral PrEP use. The study was

retrospective and comparative data for the oral PrEP cohort are not reported. The CAB-LA users were more likely to Black / African American. Additional information reported in the abstract was that in their health insurance system CAB-LA was used in 1% of PrEP users. The conference abstract provides useful context to the question of who might benefit from CAB-LA, but with limited details reported and the data coming from a USA health insurance dataset, it is unlikely the population is generalisable to NHS populations.

Two secondary analyses of study HPTN 083 were reported in conferences in 2023[29] and 2024.[30] In the 2023 abstract, US men and transgender women who have sex with men who self-identified as Black/African American or mixed race including Black were compared with Non-Black participants. Study authors suggest that access to CAB-LA can address racial disparities. The stakeholder suggests it is likely minoritised communities could see more benefit from use of CAB-LA. This is an inference from the data presented and the EAG considers it offers limited generalisable data on who might benefit from CAB-LA in clinical practice in the UK. In the 2024 abstract, choices of PrEP by geographical region (US, Latin America, Asia, Africa) were assessed. The EAG notes that there are no data regarding characteristics of the populations to answer who might benefit should CAB-LA become available.[30]

An RCT[8] of another injectable PrEP versus oral PrEP in cisgender women demonstrated that outcomes were more favourable with the injectable PrEP, as noted by the stakeholder comment. This treatment, lenacapavir, however has a different dosing schedule to CAB-LA. Also, as an RCT this does not provide evidence in an unselected group as to who may benefit from injectable PrEP, and the population is also unlikely to be generalisable.

A small study, funded by commercial and non-commercial sources, of 62 women who inject drugs who had previously had PrEP in the last month, investigated the use of long acting injectable PrEP compared with oral PrEP.[31] CAB-LA was selected in 89% and 92% of these received a first injection. Additionally, more recent injection drug use and number of sexual partners were associated with selecting CAB-LA. As a USA study of middle-aged, predominantly homeless women, the EAG highlights the likely limited generalisability to the NHS, however, the results do appear to support the choice of CAB-LA in the women studied. The EAG also notes that the

current appraisal is focused on sexually acquired HIV. Injecting drug users may acquire HIV sexually, as well as through injecting drug use.

The SLR[14] cited by the stakeholder was previously used in the CS to support the view that there is often a preference for injectable PrEP, and that this modality may help to address issues with adherence to oral PrEP. Although not formally assessed by the EAG, the quality of the SLR appears to be low risk of bias. The EAG notes that the SLRs findings on preference for injectable PrEP is 'often, though inconsistently a preference'. This was among US MSM and preferences varied more in other countries (also in MSM only) and in heterosexual, cisgender women in different countries. The finding of this SLR is not unequivocal that there is a clear indication of which groups might benefit from CAB-LA.

The BHVA reported that offering choice of PrEP is important because evidence shows that offering people at higher risk of HIV choice of PrEP intervention improves outcomes. The stakeholder cites an RCT undertaken in pregnant and postpartum women in rural Kenya and Uganda. Participants were randomised to standard of care or a dynamic choice intervention which consisted of choice of product (oral pre- or post-exposure prophylaxis), service location, HIV testing modality and person-centered care.[32] The stakeholder states that the extension to the study included the option to choose CAB-LA and that 56% chose CAB-LA and 53% oral PREP. The publication cited does not include details of any extension study and there are also no data in the NCT record for EAG to check.

Overall, the EAG considers that there are a number of issues with the studies cited including populations, methods and treatment choices and overall it is difficult to establish with certainty who might have CAB-LA in practice.

3 The impact of cabotegravir on persistence

The company states that real world evidence (RWE) supports high levels of persistence with CAB-LA, citing seven studies.[26, 28, 33-37] Six of these studies are reported as conference abstracts or posters only,[26, 28, 33, 34, 36, 37] so limited details are available. Six were conducted in the USA and one was conducted in Brazil,[26] therefore the generalisability is likely to be low. Three were funded by the company,

[33, 34, 36] the author of one had received a grant from the company,[35] and the funder was not reported in three studies.[26, 28, 37] Length of follow-up was relatively short where reported: 7 months,[34] 10 months,[33] 12 months[36] and 60 weeks.[28] One study reported 'early outcomes' only.[35] Sample size varied from 77 to 646. Different definitions of persistence were used by the studies, and the populations under study also varied.

The company reports that 81% of individuals in the OPERA cohort were still receiving CAB-LA at a median follow-up of 10 months (IQR 3–14).[33] The proportion was based on 646 (N=764, 85%) complete initiators (defined as those who had a second injection ≤60 days after the first) who missed ≥2 target windows (i.e. ≥128 days without injection), and not the whole population of people initiating CAB-LA included the study (N=764). This excludes 118/764 (15%) incomplete initiators, 56% of whom had an additional injection a median 11 weeks later. The data may therefore be biased. The poster publication does not explicitly state how many people were still receiving CAB-LA at the end of the analysis.

There is a typographical error in the company's description of the TRIO cohort,[34] it should read 83% (393/474) (not 393,474) remained on CAB-LA. Of 526 people with ≥1 injection included in the study, persistence (defined as remaining on CAB-LA at time of analysis, median follow-up 7 months) was assessed only among individuals with ≥2 injections of CAB-LA, including those who discontinued and re-initiated. The persistence calculation therefore excluded 52 people who discontinued after only one injection. Data were obtained from the TRIO HIV Research Database, but limited details of this are reported.[34]

Evidence on persistence from the OPERA and TRIO studies was also submitted by the company at Technical Engagement, and the EAG responded at that time.

In the description of an early implementation study,[35] the company's footnote states that 10% discontinued CAB-LA, with the main text stating that 90% persistence was reported among 77 CAB-LA initiators. Length of follow-up was not reported, but the EAG notes that the publication reports discontinuation under 'Early outcomes', and that the eight individuals (10%) discontinued CAB-LA after a median of just 1.5 (IQR 1–3) injections. Medium to longer term outcomes were not reported by the study.

The EAG considers that these data do not provide clear evidence of the rate of persistence.

Traeger 2025[28] defined persistence as the proportion with an injection within 10 weeks prior to each timepoint (28 weeks and 60 weeks), and this was evaluated among CAB-LA users still enrolled in the health plan at this timepoint. It is not clear how many people were no longer enrolled. The company correctly reports 78.3% and 73.0% persistence at 28 and 60 weeks. However, as data are only presented in an abstract, the EAG is unable to take into account other considerations which may be relevant to the interpretation of these data.

The PILLAR study[36] was conducted at 17 clinics for MSM and transgender men in the USA. Persistence was defined as the duration for which an individual continued to receive injections, and was reported as 85% and 72% at 6 months and 12 months, respectively. The study was funded by the company and published as an abstract only.

The company states that in the Brazilian ImPrEP study, CAB-LA significantly improved coverage and protection.[26] Coverage was defined as the proportion of persons covered by oral PrEP or CAB-LA during follow-up, but persistence data were not reported in the abstract, so this does not contribute to the evidence base on persistence.

Persistence was stated as 81.3% among 155 people who received ≥1 injection in the CAN community health network study abstract.[37] However, length of follow-up was not reported, persistence was not defined and limited details of the study participants were available for the EAG to consider the appropriateness of these data.

Two of the above seven studies cited by the company also included a cohort with oral PrEP,[28, 33] but the proportions still receiving oral PrEP at the time of analysis were not reported for comparison.

For evidence on persistence to oral PrEP ‘across a range of countries’, three studies conducted in France,[38] Belgium[39] and the USA[40] are cited by the company, but results from the first two are not discussed. The first study used data from the French National Health Data system and included 42,159 people who had initiated PrEP.[38] No prescription renewal was recorded in the first six months after initiation for 20.1%

(7148/35,549) of new PrEP users, suggesting a substantial proportion of early treatment discontinuation. However, 80-90% of users renewed PrEP from one semester to another, which the authors suggested was a good level of maintenance among those engaged in treatment. The study is considered to be reasonably representative of the NHS population by the EAG. The study in Belgium found 18.1% of 4559 PrEP users were dispensed PrEP only once in the first 6 months of PrEP use, and described characteristics associated with this.[39]

Oral PrEP Persistence in the US study, which was funded by the company, was reported as 70.2% at 6 months, and 57.4% at 12 months among individuals with ≥6 months (n=18,261) and ≥12 months (n=12,667) follow-up.[40] Mean follow-up was 504 days for FTC/TDF. Persistence was assessed using Kaplan-Meier analysis in this study, and PrEP non-persistence was defined either as a gap of >90 days between the end of the days of supply of a dispensing and the start date of the next fill or as a gap of >90 days between the end of the days of supply of the last dispensing and the end of the observation period (censored at first evidence of HIV-1). These definitions may not be comparable to other studies.

In addition, the company states 66% of 3780 individuals with ≥1 follow-up visit discontinued oral PrEP during the Brazilian ImPrEP study.[41] Median follow-up was 2.97 years; longer than the CAB-LA studies. The citation is an abstract only, so limited details are available

Lower persistence with oral PrEP was reported by Huang 2025,[42] which may be due to differences in persistence definitions or length of follow-up. In this study, which was published as an abstract only, persistence was defined as the duration of continuous PrEP prescription fills until a >30 days gap. Non-persistence was the date when the prescribed supply would be depleted if taken daily. Cohorts were followed for 12 to 36 months post-initiation. The authors concluded that ‘less than half of new oral PrEP users persisted beyond 6 months, and persistence declined over time. This trend might reflect increased use of on-demand PrEP and transitions to injectable PrEP.’

The company also refers to a global systematic review and meta-analysis.[43] The same persistence data from this study were cited in the original company submission so are not additional evidence and have not been addressed by the EAG here.

The EAG has concerns regarding the comparability of evidence between oral PrEP CAB-LA. [redacted]There is limited evidence available on persistence with CAB-LA and the EAG has concerns regarding its robustness. As stated earlier, a systematic review has not been conducted and it is unclear whether the cited studies reflect the entirety of the evidence.

The company states that at the recent advisory board, the experts suggested that [redacted]. The EAG notes that [redacted]The EAG has reservations about the appropriateness of using data from long-acting HIV treatment. The company cites one study of HIV treatment (CAB-LA with rilpivirine [RVL]) to support the data on persistence of CAB-LA PrEP. The US ABOVE study is published as an abstract only, with limited details available. The retrospective cohort study required participants to have ≥6 months follow-up; the numbers without this and numbers lost to follow-up were not reported. Persistence was measured as the number of days from index until treatment discontinuation (i.e. no claim for the index drug within 60 days after the previous days of supply was exhausted) or end of follow-up, and were not reported as proportion of people as in other studies cited by the company. There was a high standard deviation with CAB+RVL LA. The difference between groups was a mean of 43.8 days (median 18 days), but the clinical importance of this is unclear.

In the company's addendum, data from [redacted] of anonymised patient level data (APLD) is used in the company's revised base case. [44] The reference provides little context, methods or details other than top level results. [redacted]. Data presented in company's addendum are for '[redacted]

[redacted] Insufficient information is provided for the EAG to consider the reliability or generalisability of the results.

Three additional stakeholders provided comments and evidence on the impact of CAB-LA on persistence (Rachel Jones, British HIV association and National AIDS Trust); all cited evidence has already been considered above.

4 The duration of the risk period that should be modelled

Two abstracts and one confidential report from the company's expert advisory group were used to support the company assumption that 5 years is a reasonable duration of the risk period for modelling. One abstract was undertaken in the USA,[45] the other in Brazil, Peru and Mexico.[41] The sample sizes were large in both studies, 24,232 (TDF/FTC group) and 3928 respectively. Dates of the data collection in these abstracts ranged from 2019-2020 in one and 2018 to 2024 in the second.

In the USA abstract,[45] which was previously used in the original CS in relation to persistence of TDF/FTC, the EAG agrees with the company that the study shows a high rate of discontinuation of TDF/FTC (over 40% of people at 12 months). However, the remaining statements made by the company relating to the 5 year risk period is from extrapolation of this study's data. The study is a retrospective analysis. Limited methodological detail of the study or the population are reported in this abstract, which was published in 2021; it is not clear if this has been published subsequently in a peer review publication. Funding is not reported but all authors are employees of commercial pharmaceutical companies. Generalisability to the UK population is unclear. The second abstract, from a prospective single arm study undertaken in Brazil, Peru and Mexico between 2018 and 2024 was discussed above (persistence).[41] The EAG agrees that there were high levels of discontinuation with oral PrEP (66%) over a median follow-up of 2.97 years. The EAG notes that these studies are not examining whether participants are still at risk, and the relationship between persistence and risk isn't clear

The company submitted a confidential report from a recent advisory group meeting.[46] In the submission document the company summarised that experts felt [redacted]

[redacted] However, [redacted]" The EAG agrees this is stated in the report, but also note that "[redacted]. The EAG therefore has reservations that the advisory group view is that a [redacted] is reasonable. The EAG also notes that the summary from the advisory group is of opinion rather than evidence, and that no details of the advisory groups experience and level of expertise, whether clinical or academic or whether any other conflicts of interest were reported. The experts' affiliations were, however, reported.

No other stakeholders provided evidence about the high risk period.

The EAG view is that there is insufficient evidence and inconsistent expert opinion of the duration of the risk period which should be modelled.

5 Modelling of transitions from CAB-LA to oral PrEP

One stakeholder provided commentary and supporting evidence on the percentage of people who switch from CAB-LA to oral PrEP. The company cites four references to support the view that a rate of [redacted] for people who switch to TDF/FTC after discontinuing CAB-LA is reasonable. Three references relate to recent conference abstracts of RWE data and one source is from the views of experts at a company advisory group meeting. Two of the conference abstracts report data from the USA and one from Zambia. Sample sizes of those discontinuing CAB-LA but remaining at risk ranged from 24 to 29 in two studies, in the third this was not reported (see discussion below).

In the abstract by Dieterich,[47] the EAG concurs that the company's statement regarding transition rates from CAB LA to (2-1-1 or daily) oral PrEP is accurate (93% (27/29). This USA study is a retrospective study using data from electronic health records and it is unclear how participants were selected or data extracted so there is the potential for bias. Also as a US based RWE from a single site the EAG considers the generalisability to UK practice to be low. The funder of the study is not reported.

The company states that in the second USA study 35 individuals discontinued cabotegravir for PrEP and 12 had oral PrEP prescribed after discontinuation.[28] The EAG has been unable to verify these data from the published abstract; it is possible these were presented to the conference but not available on record. However, there also appear to be some other differences with the company stating the cohort size was 23,311 but in the poster the sample size reported was 19,679. The dates in the reference are reported to be from December 2021 to June 2024, and not from May 2022 to June 2024 as stated in the company submission. Furthermore, 141 (0.7%) individuals were prescribed CAB-LA and not 180 as stated in the company comments.

The abstract from Zambia presents data from two health facilities which were part of an implementation program that was run across six sites in two districts within Zambia; the EAG notes that the company states that the data are from six implementation sites. The median age was 24.4 years with a higher representation of woman than men (55.8% females of which 32.5% were adolescent girls and young women). The EAG agrees that the abstract reports that of 609 participants, 3.9% (n = 24) discontinued CAB-LA and 92% of these switched to oral PrEP. The EAG notes that 83% discontinued owing to Hepatitis B infection. These factors all suggest that the representativeness of the population is low. In addition, without more information the reliability of the data is unknown.[48]

One of the questions asked by the company to their clinical advisory group was whether some patients would transition from CAB-LA to oral PrEP in clinical practice. The company submission states that [redacted]. The EAG notes that the advisory group did not provide any indication of the proportion but [redacted]. As discussed previously, details of the advisory group and their affiliations were reported in the confidential report provided to the EAG but no other details were reported.

The EAG has reservations about the reliability and representativeness of the data sources presented by the company, but additionally the EAG view is that the company's summary of the evidence from these sources does not fully reflect the findings seen.

The National AIDS Trust cites one study to support the view that transitions from oral PrEP to CAB-LA are expected to be limited and should not significantly impact modelling. They do not provide commentary or evidence of rates of switching from CAB-LA to oral PrEP.

6 The potential for managed access

Four stakeholders provided comments on the potential for managed access. No evidence was used to support comments.

7 Commercial arrangements

No comments were provided.

8 Additional information provided: no optional oral lead-in (OLI) phase

The company provided evidence for the rationale of conducting new analyses with data from the oral lead-in (OLI) phase of the HPTN 083 and 084 trials removed. The company cites a RWE study that found 97.8% of people commencing CAB-LA for PrEP (n=270) initiated CAB-LA for PrEP directly with the injection.[49] The study, a single-centre retrospective cohort study conducted in a PrEP clinic in the MidWest US, was published as an abstract only, so limited details are available. Median age was 33 years, 80.4% were cisgender men, and 54.1% were White. Private insurance was held by 60.4%, and 29.6% were residing in a high HIV vulnerability area. The generalisability to the relevant UK population is unclear and the EAG has concerns regarding the robustness of the evidence.

The company does not provide clinical expert opinion on current or anticipated use of the optional OLI in UK clinical practice. The EAG notes this issue was not raised

at the company's advisory board meeting,[46] although it is apparent from this document that [redacted]. In the EAG report it was noted that the 'EAG clinical expert stated that in UK clinical practice, it is likely that an oral lead-in would be an option for people worried about side-effects.' It is unclear what proportion this might be.

The company states that trial results demonstrated there is a risk of HIV acquisition during the OLI due to sub-optimal adherence to oral PrEP.[50-52] However, there are concerns with these data, including whether poor adherence can be attributed to all HIV acquisitions, reporting of selected subgroups of the trials only, and the possibility that those people who did not adhere optimally to the oral phase of the trial would also have been more likely to have adherence issues in the injection phase. By excluding these people, the analysis may potentially be biased.

The EAG notes that the removal of the OLI has not been raised at an earlier opportunity during the appraisal process, and there has been no opportunity for stakeholders to comment on it.

The EAG has checked the data in Company Evidence Submission Addendum Table 2 against the original CS and CSR where possible. Post-hoc blinded analyses for the injection phase only are not available in the CSR and could not be validated by the EAG. These data are used in the [redacted] and cost-effectiveness analysis. The updated post-hoc analyses [redacted] the reduction in risk of incident acquisition relative to oral TDF/FTC from 66% in the primary analysis to [redacted] (with CAB-LA incident cases reduced from 13 to [redacted]) in study HPTN-083, and from 88% in the primary analysis to [redacted] (with CAB-LA incident cases reduced from 4 to [redacted]) in study HPTN-084. The post-hoc testing of stored plasma samples better characterises the timing of HIV acquisition during the blinded phases of Steps 1 and 2, however given their post hoc nature, these were not reproduced in the original EAG report. The company's addendum has an un-numbered Table between Tables 3 and 4: '*Indirect comparison % Effectiveness for the HPTN 083 and HPTN 084 trial populations'.* This Table has effectiveness parameters 'Submitted ITC in Document B' and '[redacted] for addendum'. However, the data 'Submitted ITC in Document B' are slightly different to the original CS (CS Table 22): addendum cabotegravir versus no PrEP (HPTN-083 population) mean [redacted], CS Table 22 mean

[redacted]; addendum cabotegravir versus no PrEP (HPTN-084 population) mean [redacted], CS Table 22 mean [redacted]. The company explained that the reason for the differences is because the company was referring to updated ITC values submitted in the response to draft guidance, not the values originally submitted in document B.

The EAG used the inputs as described by the company in their addendum, and applied these to the previous version of the economic model. The results were very similar with identical QALY estimates, but minor differences for cost estimates. The magnitude of difference was <£5 for both arms.

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Single Technology Appraisal

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

EAG and DSU report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by 5pm on 11th June 2025 using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as ’confidential’ should be highlighted in turquoise and all information submitted as ‘depersonalised data’ in pink.

Contents

Evidence Assessment Group (EAG) report

Issue 1 Clarity and accuracy

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 4 The EAG state: "*Both the BHIVA and the National AIDs Trust cite data from the ImPrEP CAB study, which was sponsored by the company"* This is incorrect. ImPrEP was not sponsored by ViiV. ViiV provided study drug on the request of the study sponsor. The study sponsor is Fundação Oswaldo Cruz (Fiocruz) and funder is UNITAID.	Please remove the part of the statement reporting the company sponsored the ImPrEP study.	The statement is inaccurate.	Text amended to state 'which was supported by the company'.
Page 4 The EAG state: *"This was, however, a selected group and may not offer any information about who might have CAB-LA in practice"* These data are from an implementation science study, and therefore does address the question of who might receive cabotegravir in practice within the Brazilian public health system. The study population comprised men who have sex	Please remove this statement.	The statement is inaccurate.	Not a factual inaccuracy. This is an interpretation issue. The EAG focus was on who might have CAB-LA in UK practice, in the real world rather than from a selected group of people recruited to a cohort study.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
with men, non-binary or transgender persons with a negative HIV test result, aged 18–30 years who are PrEP naïve across six public PrEP services in six Brazilian cities.			
Page 4 The EAG state: *"There are also no details of how the choices were presented to these individuals"* The conference slides, published online, state that choice was offered following HIV and STI testing as part of local standard of care.	Please amend the statement to: "*Choices were presented as part of local standard of care, following HIV and STI testing*".	Statement is inaccurate; the information is available in the published conference slides.	Not a factual inaccuracy. This statement refers to the lack of detail as to how the PREP options were presented to the participants to allow them an informed choice, e.g. information about how they are administered, effectiveness, side effects etc.
Page 4 The EAG state: *"the representativeness of this population to the NHS is likely low."* Regardless of geographical location, it is expected that people at high risk of HIV acquisition with PrEP need, coming to sexual health services (SHSs), will have similar HIV prevention needs.	Please remove this statement.	The statement is inaccurate; it is expected that people at high risk of HIV acquisition with PrEP need, coming to SHSs, will have similar HIV prevention needs regardless of geographic location.	Not a factual inaccuracy, this is the opinion of the EAG.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 4 The EAG state: *"The full publication that was cited doesn't appear to report these data.[2]"* The full publication was published in 2023. The data the statement is referring to were reported in a 2025 CROI abstract (https://www.croiconference.org/abstract/3614-2025/), published subsequent to the full 2023 publication.	Please remove the statement or note that these data were subsequently made available in the published abstract.	The data are published in the 2025 abstract.	The data the EAG are referring to are the details of how choices were presented to the participants. This information is not presented in the full paper or subsequent abstract. No change made.
Page 5 The EAG state: *"In the 2023 abstract, US participants who self-identified as Black/African American or mixed race including Black were compared with Non-Black participants."* The current statement is missing key information regarding the study population.	Please amend to: *"In the 2023 abstract, US men and transgender women who have sex with men who self-identified as Black/African American or mixed race including Black were compared with Non-Black participants."*	To provide clarity around the study population.	Additional information added as requested.
Page 5 The EAG state: *"The stakeholder states that results suggest it is likely that minoritised communities, will see more benefit from use of CAB-LA. This is an*	Please amend to: "Study authors suggest that access to CAB-LA can address racial disparities. The stakeholder suggests it is likely minoritised	The statement is inaccurate, study authors have identified the role CAB-LA can play in addressing the needs of minoritised communities.	First sentence amended as requested. The second sentence has been retained as this is EAG opinion.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
inference from the data presented and the EAG considers it offers limited generalisable data on who might benefit from CAB-LA in clinical practice in the UK."	communities could see more benefit from use of CAB-LA."		
Page 5 The EAG state: *"The EAG notes that there are no data regarding characteristics of the populations to answer who might benefit should CAB-LA become available."* These data are reported in the abstract table. In addition, the statement is missing the citation.	Please remove this statement and accurately reflect the results reported by the study. Please also include the citation for the study within the statement.	It is incorrect to state these data are not reported.	The citation has been added. However, there is not a table of characteristics in the abstract so no further change made.
Page 5 The EAG state: "*This treatment, lenacapavir, however has a different dosing schedule to CAB-LA and therefore results may not be applicable to the current appraisal questions*". The PURPOSE 1 trial did demonstrate that the oral arms were no different to the background HIV incidence rate in the study population as a whole due to sub-optimal adherence to oral PrEP. This is not related to the dosing interval	Please amend to: "This treatment, lenacapavir, has a different dosing schedule to CAB-LA"	The statement is inaccurate.	Sentence amended as requested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
of the long-acting injectable LA arm, and therefore has transferability to CAB-LA.			
Page 5 The EAG state: *"The EAG also notes that the current appraisal is focused on sexually acquired HIV."* It is important to note that people who inject drugs can also acquire HIV through sexual routes of transmission. In addition populations of people who use drugs face significant social stressors and may find it challenging to adhere to oral therapy, and have expressed a need for long-acting injectable PrEP. The current statement inaccurately implies that the study is not relevant to the appraisal population.	"The EAG also notes that the current appraisal is focused on sexually acquired HIV. *Injecting drug users may acquire HIV sexually*".	Amended for clarity.	The EAG notes that the inclusion of a study of drug users in the company's ITC was raised as a Key Issue in the original ERG report. Sentence amended as requested with an additional caveat: 'Injecting drug users may acquire HIV sexually, *as well as through injecting drug use'*
Page 6 The EAG state: *"The publication cited does not include details of any extension study and there are also no data in the NCT record for EAG to check."* These data have been subsequently published: Kamya MR et al. Dynamic choice HIV prevention with cabotegravir long-acting injectable in rural Uganda and Kenya: a	Please note that these data have been subsequently published.	These data are published.	Correct at time of writing, no change made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
randomised trial extension. Lancet HIV 2024; 11: e736-45 https://doi.org/10.1016/S2352-3018(24)00235-2			
Page 7 The EAG state: *"As described in the company's footnote, the proportion was based on 19% (124/646) of complete initiators (defined as those who had a second injection ≤60 days after the first) who missed ≥2 target windows (i.e. ≥128 days without injection), and not the whole population of people initiating CAB-LA included the study (N=764). This excludes 118/764 (15%) incomplete initiators, 56% of whom had an additional injection a median 11 weeks later. The data may therefore be biased."* Persistence was based on complete initiators. These results remain relevant, since not all would want to continue injectables after they have experienced them and they may choose not to complete their initiation. This data then looks at persistence amongst those who have completed it and are now in maintenance phase.	Please amend to: "As described in the company's footnote, the proportion was based on 85% (651/770) of complete initiators (defined as those who had a second injection ≤60 days after the first) who missed ≥2 target windows (i.e. ≥128 days without injection), and not the whole population of people initiating CAB-LA included the study (N=764). This excludes 118/764 (15%) incomplete imitators, *56% of whom had an additional injection a median 11 weeks later*."	The statement is inaccurate.	The EAG is unable to identify data stating 81% still received CAB-LA at the end of analysis in the citation provided, and assumed from the company's footnote that it was calculated from the 19% data reported; i.e. of 646 complete initiators, 124 (19%) missed ≥2 target windows, and 552 (81%) did not and were (presumably) still receiving CAB-LA. The EAG acknowledges that '*the proportion was based on 19% (124/646) of complete initiators'* is not correct. However, the company asks the sentence to be amended to 85% (651/770), but the numerator and denominator are not stated

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			in the citation; the number of completer initiators is reported as 646/764. The sentence has been changed as follows: '*The proportion was based on 646 (N=764, 85%) complete initiators (defined as those who had a second injection ≤60 days after the first) who missed ≥2 target windows (i.e. ≥128 days without injection), and not the whole population of people initiating CAB-LA included the study (N=764).* The sentence *'The data may therefore be biased'* is EAG opinion and not a factual error and has not been removed.
Page 7 The EAG state:	Please amend to: "*The persistence calculation therefore*	Amended for clarity.	Not a factual error, no change made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"*The persistence calculation therefore excluded 52 people who discontinued after only one injection*." This data remains relevant particularly given that ongoing persistence for oral PrEP has been lower. Injectables are not going to be acceptable to everyone, and this data represents persistence among those who initiate and continue.	*excluded 52 people who discontinued after only one injection, reflecting people who initiated and continued CAB-LA*"		
Page 14 The EAG state: *"The National Aids trust cites one study to support the view that transitions from oral PrEP to CAB-LA are expected to be limited and should not significantly impact modelling. "* Typographical error in the order of the interventions in the statement.	Please add the relevant citation and update the text to: "*that transitions from CAB-LA to oral PrEP are expected to be limited and should not significantly impact modelling"*	Amended for accuracy.	The EAG has reviewed the National AIDS Trust's response to NICE consultation, and the EAG's understanding is that they are referring to the switch from oral PrEP to CAB-LA. The response goes on to say 'Where switching does occur, data from the PILLAR study and others indicate retention and minimal discontinuation'. No change made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13 The EAG state: "*The company states that in the second USA study 35 individuals discontinued cabotegravir for PrEP and 12 had oral PrEP prescribed after discontinuation.[28] The EAG has been unable to verify these data from the published abstract; it is possible these were presented to the conference but not available on record. However, there also appear to be some other differences with the company stating the cohort size was 23,311 but in the poster the sample size reported was 19,679. The dates in the reference are reported to be from December 2021 to June 2024, and not from May 2022 to June 2024 as stated in the company submission. Furthermore, 141 (0.7%) individuals were prescribed CAB-LA and not 180 as stated in the company comments."* Data provided from conference oral presentation slides.	Please amend to: "Of 35 people who discontinued CAB-LA, oral PrEP was prescribed to 12 (34%) after discontinuation and 2 (6%) during CAB-LA use".	The data are presented at the 2025 CROI conference.	Thank you for the additional information, however the company has not provided the conference oral presentation slides or a link to these. No change made as the EAG is unable to verify the data.
Page 15 The EAG state: *"However, the data 'Submitted ITC in Document B' are slightly different to the original CS (CS*	Please amend to: "The reason for these differences is because the Company were referring to updated ITC values	Updated for clarity	Amended to 'The company explained that the reason for the differences is because the company was referring to updated ITC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 22): addendum cabotegravir versus no PrEP (HPTN-083 population) mean [redacted] *CS Table 22 mean* [redacted] *addendum cabotegravir versus no PrEP (HPTN-084 population) mean* [redacted]*, CS Table 22 mean* [redacted]*. The reason for these differences is not clear."* The values referred to by the EAG represent the original ITC results, while the addendum refers to the corrected values submitted in the 'Company Response to DG' on Oct 17th 2024	submitted in the response to draft guidance, not the values originally submitted in document B".		values submitted in the response to draft guidance, not the values originally submitted in document B.'

Issue 2 Incorrect reference

Description of problem	Description of proposed amendment	Justification for amendment	
Page 4 The EAG state: *"The EAG concurs that the conference abstract reports that majority, 83%, chose CAB-LA.[2]"* The reference provided does not support this statement	Please amend the following reference: "26. Coutinho C, Grinsztejn B, Hoagland B, Cunha M, Leite I, Ismério R*, et al.* PrEP Use Trajectories and HIV Incidence Among PrEP Users in Brazil:	Reference does not support the statement	Typographical error, correct reference now cited.

Description of problem	Description of proposed amendment	Justification for amendment	
	Findings From the ImPrEP Study. Astract 1347 presented at CROI 2025. . Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); San Francisco, CA. , March 9-12, 2025. URL: https://www.croiconference.org/abstract/3474-2025/" To "ImPrEP CAB Brasil: Enhancing PrEP Coverage With CAB-LA in Young Key Populations. Abstract 192 presented at CROI 2025. March 9-12, 2025. San Francisco, CA. Available at: https://www.croiconference.org/abstract/3614-2025/ (last accessed June 2025)"		

Issue 3 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	
Page 3–4, typographical error	Please amend: "collective view that CAB-LA may improve update of PrEP" to "collective view that CAB-LA may improve uptake of PrEP".	Amended for clarity.	Typographical error corrected.
Page 4, typographical error	Please amend: "National AIDs Trust" To "National AIDS Trust".	Amended for clarity.	Typographical error corrected.

References

1. Hanum N, Cambiano V, Sewell J, Rodger AJ, Nwokolo N, Asboe D, et al. Trends in HIV incidence between 2013-2019 and association of baseline factors with subsequent incident HIV among gay, bisexual, and other men who have sex with men attending sexual health clinics in England: A prospective cohort study. PLoS Med. 2021;18(6):e1003677.

A REVIEW OF THE BASELINE RISK OF HIV ACQUISITION IN PEOPLE WHO WOULD BE ELIGIBLE FOR CABOTEGRAVIR OR THE COMPARATORS

REPORT BY THE DECISION SUPPORT UNIT

May 2025

Author: Brian Rice

Sheffield Centre for Health and Related Research, University of Sheffield

Decision Support Unit, SCHARR, University of Sheffield, Regent Court, 30 Regent Street

Sheffield, S1 4DA

Tel (+44) (0)114 222 0734

E-mail dsuadmin@sheffield.ac.uk

Website www.nicedsu.org.uk

X @NICE_DSU

Brian Rice, is an HIV epidemiologist focusing on incidence measurement in eastern and southern Africa. He was previously the HIV Principal Scientist at the Health Protection Agency and Public Health England, responsible for developing new surveillance platforms and novel analytical methods to better define HIV epidemics in the UK and EU.

ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) External Assessment Centre is based at the University of Sheffield with members at York, Bristol, Leicester and the London School of Hygiene and Tropical Medicine. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Centre for Health Technology Evaluation Programmes. Please see our website for further information www.nicedsu.org.uk.

The production of this document was funded by the National Institute for Health and Care Excellence (NICE) through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

This report should be referenced as follows:

Rice B. (2025) A review of the baseline risk of HIV acquisition in people who would be eligible for cabotegravir or the comparators. Report by the Decision Support Unit.

ABBREVIATIONS AND DEFINITIONS

AIDS	Acquired Immune Deficiency Syndrome
aOR	Adjusted Odds Ratio
CI	Confidence Intervals
CRI	Credible Intervals
EAG	External Assessment Group
GBMSM	Gay, Bisexual and Men who have Sex with Men
GUMCAD	Genitourinary Medicine Clinic Activity Dataset
HIV	Human Immunodeficiency Virus
MSM	Men who have Sex with Men
PrEP	Pre-exposure Prophylaxis
PY	Person-years
STI	Sexually Transmitted Infections
TGW	Transgender Women
UK	United Kingdom
UKHSA	United Kingdom Health Security Agency

EXECUTIVE SUMMARY

Pre-exposure prophylaxis (PrEP) is a highly effective prevention tool, particularly when taken and adhered to as prescribed and when implemented as part of a strategy that includes biomedical, behavioural, and structural interventions to reduce new HIV infections. PrEP consists of antiretroviral therapies that block HIV from replicating in CD4 cells, the primary target of the virus. One such antiretroviral therapy is Cabotegravir. The National Institute for Health and Care Excellence (NICE) is currently reviewing a submission to demonstrate the clinical and cost-effectiveness of Cabotegravir for HIV PrEP to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg.

The appraisal committee remains highly uncertain on the value that should be used in the model for baseline risk of HIV acquisition. The model uses two separate baseline risk values; one for men who have sex with men (MSM) and transgender women (TGW) and another for cisgender women. With MSM/TGW making up 96.8% of the modelled population, this review focuses on the evidence submitted to NICE to recommend a plausible baseline risk in this group. This review also considers evidence in relation to a plausible baseline risk among cisgender women, and the length of the risk period.

Based on the evidence, we suggest the NICE External Assessment Groups (EAG) preferred estimate of 0·95 per 100 person-years is reasonable as a baseline for risk among MSM in the UK. With an absence of TGW specific estimates, it is recommended this MSM estimate be adopted as a proxy for this group. Although the EAG noted that the figure of 0.95 was likely to be an underestimate of baseline risk for people who would receive cabotegravir, this review highlights that it is higher than the 2022/23 Genitourinary Medicine Clinic Activity Dataset (GUMCAD) MSM estimate of 0.43 per 100 person-years and a MSM clinic-based cohort estimate of 0.71 per 100 person-years between 2013 and 2019 (methods and limitations underlying these estimates are presented in sections 4.1.1 and 4.1.3).

In relation to the most plausible value for baseline risk among cisgender women, incidence estimates for heterosexuals (2013; 0.05%), and black African heterosexual men and women (2013; 0.19%) are presented as a proxy for this group (there was an absence of cisgender women specific estimates). Reviewing these estimates in the context of contemporary incidence estimates for MSM (2013; 1.46% and 1.47%) and time trends in new HIV diagnoses in the UK (2014 diagnoses among MSM exceeded those among heterosexuals (2,975 v 2,150, respectively); 2023 this had been reversed (1,377 v 3,579, respectively)), a crude estimate of baseline risk of 0.5 per 100-person years is recommended. This review highlights differences in risk between the two most at-risk groups in the UK; MSM and black African heterosexuals.

Due to the absence of routinely available, timely, and robust data to inform sub-population specific differentiations relating to other risk factors presented in the evidence to NICE (for example, an

ability to take oral PrEP, risk behaviours, and partner information), it is recommended to proceed with baseline estimates for the two most at-risk populations and for whom estimates are available: namely, MSM (proxy for TGW) and black-African heterosexuals (proxy for cisgender women). In considering whether the at-risk period should be five or ten years, a review of age-stratified incidence estimates suggests the adoption of a ten-year period.

CONTENTS

FIGURES

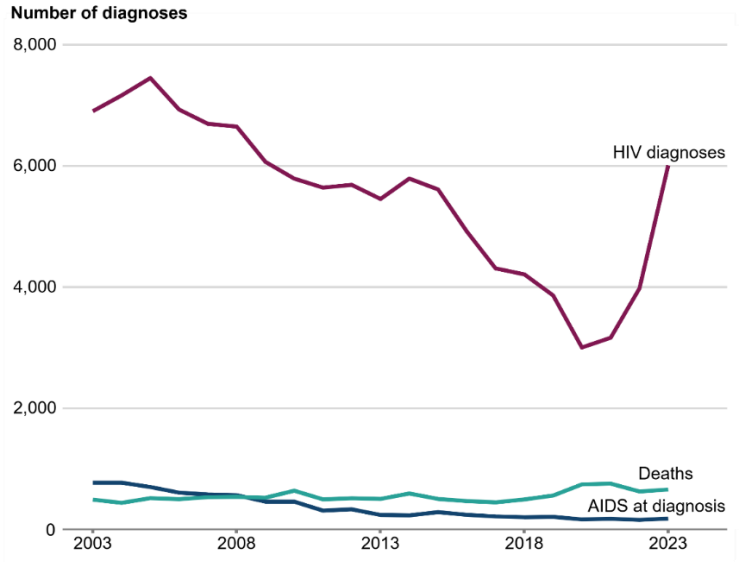
1. INTRODUCTION

The UK has a concentrated HIV epidemic where HIV transmission is elevated among defined subpopulations as compared to the general population. Ongoing rates of HIV transmission in the UK are driven by failures in ensuring people at risk of acquiring HIV have access to effective HIV prevention, people living with HIV receive a timely diagnosis, and people diagnosed with HIV are in receipt of optimal treatment to ensure sustained viral suppression.

In 2023, an estimated 113,500 people were living with HIV in the UK. Among 6,008 people newly diagnosed with HIV in England in 2023, 2,810 (47%) were first diagnosed in England (a proxy for within country transmission).[1,2] Of the 2,529 (90%) people first diagnosed with HIV in England in 2023 for whom country of birth was recorded, 1,723 (68.1%) were born abroad.[1,2] Of the 2,304 (82%) people first diagnosed with HIV in England in 2023 for whom probable route of exposure was reported, 811 (35.2%) were among men who have sex with men (MSM), and 1,386 (60.2%) were among people exposed through sex between men and women.[1,2] Of the 1,252 heterosexuals for whom ethnicity was recorded, 688 (55%) were of black African ethnicity.[1,2]

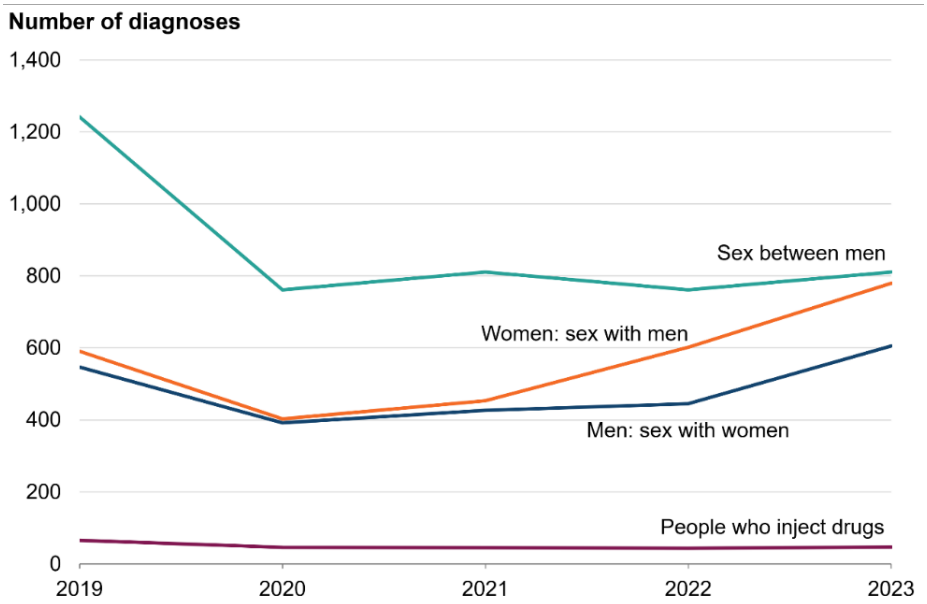
In England, following a long period of year-on-year declines in diagnoses, there has been a recent rise in diagnoses from 3,859 in 2019 to 6,008 in 2023 (Figure 1).[1] Figure 2 highlights that this increase is concentrated among heterosexual men and women, and figure 3 highlights how the increase is driven by diagnoses among people previously diagnosed abroad (the majority of whom are heterosexual).[1]

Figure 1: HIV diagnoses, AIDS at diagnosis, and all-cause deaths in people with HIV, England, 2003 to 2023[1]



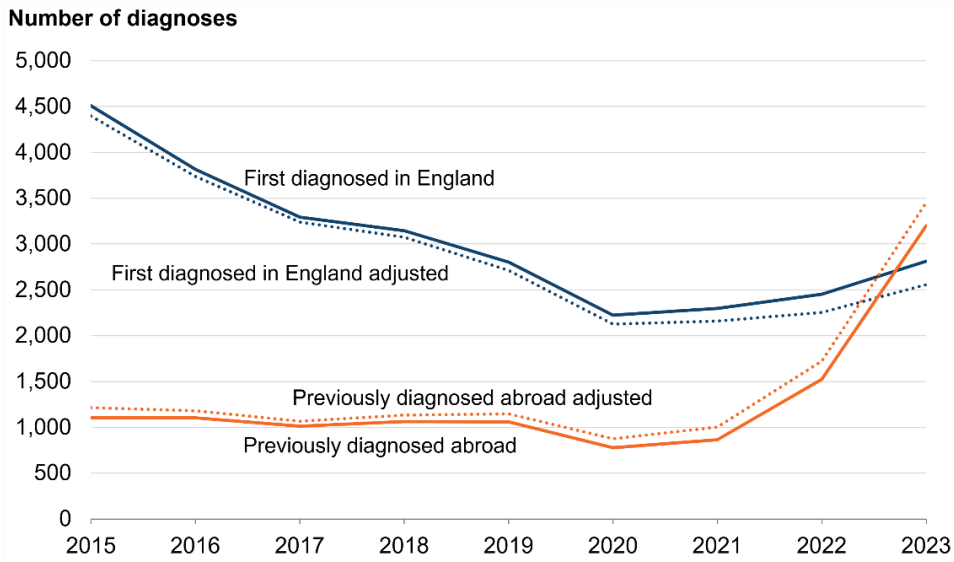
Source: Data from routine returns to the HIV and AIDS Reporting System (HARS) (New HIV diagnoses, AIDS, deaths and people in care in England of the accompanying data tables).

Figure 2: New HIV diagnoses among people first diagnosed in England by probable route of exposure, England, 2019 to 2023[1]



Source: Data from routine returns to the HIV and AIDS Reporting System (HARS) (New HIV diagnoses, AIDS, deaths and people in care in England of the accompanying data tables).

Figure 3: HIV diagnoses by country of first diagnosis including adjustments for potential misallocation of location of first diagnosis, England, 2015 to 2023[1]



Source: Data from routine returns to the HIV and AIDS Reporting System (HARS) (New HIV diagnoses, AIDS, deaths and people in care in England of the accompanying data tables). The dotted lines represent the number of new diagnoses by country of first diagnosis after adjusting for the 253 people who were reported as first diagnosed in England but were likely previously diagnosed abroad based on being born abroad.

In summary, HIV diagnoses and transmission in the UK continue to be concentrated among MSM and heterosexuals of black African ethnicity. Recent increases in diagnoses are primarily driven by diagnoses among heterosexuals who have previously been diagnosed abroad.

2. THIS REVIEW

In relation to plausible baseline risks, this review considers the evidence submitted to the first (ACM1) and second Appraisal Committee Meetings (ACM2). In particular, the review considers the company's original submission to ACM1, the ACM1 and 2 committee papers, ACM2 part 1 final slides to PM for committee, and additional evidence submission to ACM2 by the company, the National AIDS Trust, the British HIV Association, the UK Health Security Agency (UKHSA), and a clinical expert. As guided by the submitted evidence, where relevant, this review considers newly generated evidence.

In summary, the company recommended to ACM2 the adoption of a baseline incident rate of 3.9 per 100 person-years (PY) based on the Genitourinary Medicine Clinic Activity Dataset (GUMCAD) 2014 reported value for MSM who had a rectal bacterial Sexual Transmitted Infections (STI) and an HIV test in the past 12 months. The EAG recommended a baseline risk of 0.95 per 100PY for the whole population eligible for cabotegravir as informed by UKHSA draft guidance. This guidance was, in turn, informed by estimates arising from the Pre-exposure prophylaxis (PrEP) Impact Trial conducted in England 2017 to 2020 among non-trial participants.[3] The clinical expert suggested an appropriate baseline risk of 2.9 per 100PY, as informed, in-part, by the PURPOSE 1 trial funded by Gilead, which assessed the efficacy of lenacapavir and TAF/FTC by comparing the incidence of HIV infection with the estimated background incidence in the screened population.[4] At the ACM2 it was noted that this study was conducted in adolescent girls and young women in South Africa and Uganda, settings markedly different to UK clinical practice.

The appraisal committee remains highly uncertain on the value that should be used in the model for baseline risk of HIV acquisition (the model uses two separate baseline risk values; one for men who have sex with men (MSM) and transgender women (TGW) and another for cisgender women). With MSM/TGW making up 96.8% of the modelled population, this review focuses on the evidence submitted to NICE to recommend a plausible baseline risk in this group. This review also considers evidence in relation to a plausible baseline risk among cisgender women, and the length of the risk period.

As informed by available data, geographies will interchange between the UK and England. Where appropriate I will refer to gay and bisexual men as MSM and people who were exposed through sex between men and women as heterosexuals. Due to an absence of TGW specific estimates, estimates for MSM are presented as a proxy for this group. Due to an absence of cisgender women specific estimates, estimates for black African heterosexuals are presented as a proxy for this group.

For this review, we assume incidence estimates derived in sub-Saharan Africa (a focus for such measurement), where both the prevalence and incidence of HIV are greatly elevated as compared to the UK, and from which a high number of people diagnosed in the UK originate, are not

generalisable to our context. For example, it would be challenging to extrapolate current incidence estimates from Zimbabwe (0.45% among adults aged 15-49 years in 2019/20),[5] or South Africa (0.48% among all persons aged ≥2 years in 2017),[6] two countries with which the UK has strong migration ties, given differences in the prevalence of early infection in the population (probably lower in the UK due to a high proportion of infections being acquired abroad)[1,2] and sustained viral suppression (probably greater in the UK due to higher levels of sustained treatment adherence).[1,2,7] We therefore, for example, do not consider results of the HPTN 084 phase 3 trial conducted in seven sub-Saharan Africa countries,[8] or the PURPOSE 1 phase 3 trial.[4]

3. METHODS FOR ASSESSING BASELINE RISK OF HIV ACQUISITION

The evidence presented to NICE in relation to baseline risk focused on HIV incidence estimation. HIV incidence is one of a few methods at our disposal to identify individuals and populations at high risk of HIV infection to link them to effective HIV prevention. Before focusing on HIV incidence estimation, other key methods are presented / reviewed.

3.1. HIV PREVALENCE ESTIMATES

Historically HIV prevalence estimates have provided baseline estimates of the likelihood of HIV-negative individuals being exposed to the potential risk of acquiring infection. For example, in the UK, population-level HIV prevalence estimates have informed indirect HIV incidence estimation methods. However, increases over time in the number of people newly diagnosed in the UK who probably acquired the infection abroad (and thereby most likely experienced early HIV infection abroad; the period during which a disproportionate number of HIV transmissions originate),[1,2] and increases in those attaining viral suppression through the provision of optimal treatment (in 2023, an estimated 96.2% of people in England with diagnosed HIV had an undetectable viral load, reducing their risk of sexual transmission of infection to almost zero),[9,10] have resulted in the link between HIV prevalence and risk of acquiring HIV in the UK weakening. Estimates of diagnosed prevalence (number of new HIV diagnoses per year per 1,000 population) do continue to inform HIV testing strategies.[11]

3.2. TRENDS IN HIV DIAGNOSES / TEST POSITIVITY

Trends in the number of new HIV diagnoses are a poor proxy for risk as they neither denote current rates of incidence or the probability for ongoing transmission. Among people newly diagnosed with HIV in 2023 who were first diagnosed in England, four in ten were diagnosed late (CD4 cell count <350 cells per mm^3 within 91 days of diagnosis and no evidence of a recent infection),[1,2] highlighting how new diagnoses include people who acquired their infection years prior (UKHSA acknowledge that this proportion is likely to be an underestimation due to people who were actually first diagnosed abroad being misclassified as being first diagnosed in England).

Trends in HIV test positivity (percentage of all tests conducted that are positive) are also challenging to interpret in the context of assessing background risk. For example, as influenced by factors such as changing testing patterns (including changes in repeat testing), testing coverage, and knowledge of HIV status, test positivity can decrease whilst seroconversion rates either remain unchanged or increase.[12]

3.3. RISK ASSESSMENT TOOLS

Assessment of risk can be challenging both for individuals accessing health services and for those delivering them. Various tools have been developed to support clinicians in proactively identifying individuals who could benefit from PrEP through HIV risk assessment. A commonly developed and applied tool is the HIV risk score, which combines quantitative data on multiple prognostic factors into a single score. The authors of a 2022 systematic review and meta-analysis of risk scores for predicting HIV incidence among adult heterosexual populations in sub-Saharan Africa concluded that such scores had low-to-moderate discriminatory ability and uncertain generalizability, limiting their programmatic utility.[13] The authors of a proposed systematic review of HIV risk assessment tools for identifying individuals who could benefit from PrEP suggest risk assessment tools are often population and context specific.[14] They argue that key performance characteristics may change over time, even within the same population and geographic context, as the expansion of HIV treatment and other prevention tools changes the epidemiology of HIV and, hence, the risk of infection.[14]

In relation to assessing a persons likely place of infection (a key risk descriptor in the UK context), HIV treatment clinic staff have indicated that it is often unclear where a person has acquired infection due to complex sexual and migration histories spanning many years.[15] A review of a new data-informed method to assign likely place of HIV infection among people born abroad and diagnosed in the UK suggested reporting of HIV-acquisition abroad by diagnosing clinicians was significantly over estimated.[15] Potential reasons for clinic staff misclassifying risk of HIV transmission included the long incubation period of HIV, the underreporting of high-risk sexual behaviours due to social desirability bias or associated stigma, and multiple sexual partnerships over time.[15] These results align with those of a 2009 study of people of African origin newly diagnosed in London that reported clinic-based assessments to underestimate within-UK risk of HIV acquisition.[16]

3.4. INCIDENCE ESTIMATION IN THE UK

As a disproportionate number of HIV transmissions originate from people who have early HIV infection, targeting effective prevention and behavioural interventions within populations presenting with incident infections can help reduce overall levels of transmission. Although HIV incidence estimation is seen as the holy grail of risk measurement, there remains a widespread absence of HIV incidence data at a time when the interpretation of prevalence trends is becoming

ever more complex and our confidence in risk assessment tools is waning. As will be highlighted in section 4, multiple approaches to estimating HIV incidence in the UK have previously been developed and applied. These methods present incidence as against PYs (a unit of measurement used to quantify the amount of time a person or a group of people have been exposed to HIV over a specified period), as a percentage of a population at risk that develops HIV within a specific time period (usually annual) or, where population denominators are difficult to attain, as a number of infections. Depending on the method applied, differing estimates of incidence among the same / similar population can be derived.[17-19]

4. OUTSTANDING QUESTIONS RELATING TO BASELINE RISK

4.1. WHAT IS THE MOST PLAUSIBLE VALUE FOR BASELINE RISK AMONG MEN WHO HAVE SEX WITH MEN AND TRANSGENDER WOMEN?

The submission under review by NICE relates to the clinical and cost-effectiveness of cabotegravir for HIV PrEP to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg. To inform overall baseline risk, we explore incidence estimates among MSM. With an absence of TGW specific estimates, MSM estimates are presented as a proxy for this group

4.1.1. Genitourinary Medicine Clinic Activity Dataset (GUMCAD)

GUMCAD is the national mandatory STI surveillance system in England that collects data of all attendances, HIV tests, and HIV and STI diagnoses.[20,21] Electronic, pseudonymised patient-level data are collected from all commissioned sexual health services, of which there are approximately 400.[20,21] A detailed description of GUMCAD has been published in Eurosurveillance.[22]

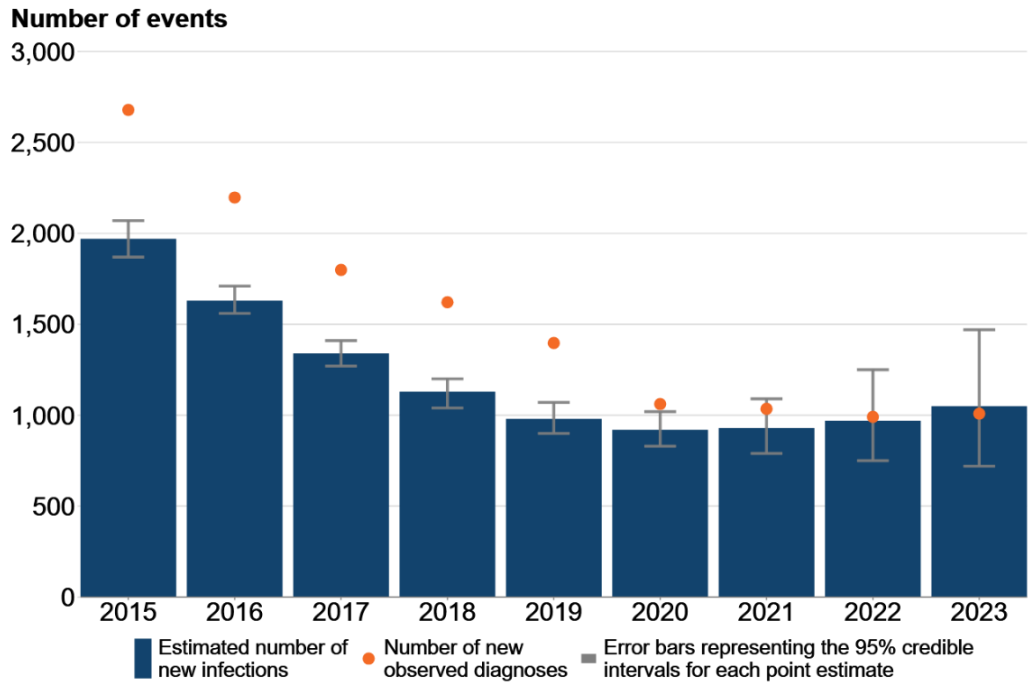
As part of this consultation, the UKHSA has provided updated GUMCAD estimates to those for 2014 which informed initial committee discussions.[21] A Kaplan-Meier analysis (a statistical approach for estimating cumulative survival probabilities) of GUMCAD data was conducted to estimate annual HIV incidence rates per 100 person-years amongst on gay, bisexual, and other men who have sex with men (GBMSM) attending sexual health services in England between 2014 and 2023.[21] GBMSM were followed up from their first HIV test in the year of interest until their last attendance or until they were newly diagnosed with HIV within 365 days of their first HIV test in that year. This analysis therefore restricts the study population to GBMSM with at least two HIV tests within the follow-up period. In 2022/23 estimated HIV incidence amongst GBMSM with a rectal bacterial STI in the previous year was 0.59 per 100PY (95% Confidence Intervals (CI) 0.37-0.94), and 0.43 per 100PY (95%CI 0.22-0.87) amongst those with a rectal bacterial STI diagnosis and a HIV test in the UK in the previous year. The lower of these two estimates reduces the potential inclusion of people who may have already been diagnosed with HIV outside of the UK.[21]

4.1.2. CD4 Back Calculation

In the UK, the back calculation of CD4 cell counts at diagnosis (a type of white blood cell that indicates HIV disease progression in an individual) has been the mainstay of HIV incidence estimation.[23-25] Incidence estimates are reconstructed in a given population using information on observed numbers of HIV diagnoses over time, CD4 count distribution at or soon after diagnosis, and information on disease progression attained on population trend analysis of CD4 cell counts between diagnosis and commencing treatment. Recent declines / challenges in CD4 cell count surveillance at diagnosis, and a reduction over time in the length of period between diagnosis and commencing treatment, have reduced our capacity to operationalise back calculation methods.[26]

Based on an age-stratified CD4-staged Bayesian back-calculation model among adult MSM in England 2009 to 2018, a steep decrease in the annual number of new infections was reported from 2770 (95%CrI 2490–3040) in 2013 to 1740 (95%CrI 1500–2010) in 2015, followed by a steadier decrease down to 854 (95%CrI 441–1540) in 2018.[25] Although this decline was estimated in all age groups, it was particularly marked among MSM aged 25 to 34 years, and slowest in those aged 45 years or above. An aligned CD4 analysis highlighted a sustained decline between 2011 (2,700; 95%CrI 2,520-2,850) and 2019 (540; 95%CrI 180-1,810).[27] A more recent application of the CD4-based method suggests that this decline in incidence up to 2019 was followed by a plateau and then a slight rise in incidence up to 1,050 (95%CrI 720-470) new infections in 2023, which was not statistically significant (Figure 4).[2]

Figure 4: Estimated number of new infections using a CD4 back-calculation method, and new observed diagnoses in GBMSM, England, 2015 to 2023[2]



Source: CD4 back-calculation model, using data from routine returns to HANDD[2]

4.1.3. Prospective Cohort Study / Trial

Incidence was calculated among GBMSM recruited prospectively through one of three large sexual health clinics in London and Brighton (56 Dean Street, London; Mortimer Market Centre, London; and Claude Nicol Clinic, Brighton) who presented for routine STI or HIV testing, were initially HIV–negative, and self-completed a baseline and subsequent four-monthly and annual questionnaires.[28] Incident HIV was ascertained using information collected through online follow-up questionnaires and via data linkage with national HIV surveillance data. For each study participant with a matched record, information on date and region of HIV diagnosis, CD4 and viral load at HIV diagnosis, and if relevant, time from diagnosis to linkage to care, time from diagnosis to treatment initiation, and death was collected. All participants reported as being newly diagnosed in a follow-up questionnaire were identified as having a new HIV diagnosis in the linked data. Data linkage also identified three participants who were positive at entry to the study; they were excluded from analysis. Incident HIV infection was defined as seroconversion from HIV–negative status at baseline to HIV–positive during follow-up. Person-years of follow-up was calculated from date of baseline questionnaire until either date of HIV diagnosis for those seroconverting or three months before date of data linkage completion for those not seroconverting.[28]

The authors of this study reported an overall HIV incidence rate of 0.71 per 100 PY (95% CI 0.51 to 1.00) between 2013 and 2019, with a suggestion of a decline in incidence over the study period (from 1.47 (95% CI 0.48 to 4.57) per 100 PY in 2013/2014 to 0.25 (95% CI 0.08 to 0.78) per 100 PY in 2018/2019).[28] Baseline and longitudinal reported PrEP use by study participants was not shown to be associated with reduced HIV incidence. At baseline, 5% of participants reported PrEP use in the past 12 months. The authors suggest this low percentage may reflect early PrEP takers who are having high-risk sexual behaviour.

In acknowledging limitations of their study, the authors highlight that their clinic-based cohort was predominantly highly educated, employed, in a stable economic situation, and of white ethnicity and, therefore, may not be representative of the broader MSM population.[28] The authors also suggest a lack of association between incidence and PrEP use may be due to such use decreasing risk of HIV acquisition whilst also acting as an indicator of very high-risk behaviour.

The prospective, open-label, single-arm, multicentre PrEP Impact trial conducted at 157 sexual health services across England between October, 2017, and July, 2020 estimated incidence among MSM to be 0·13 (95% CI 0·08–0·19) per 100PY in trial participants and 0·95 per 100PY (95% CI 0·88–1·03) in non-trial attendees.[3]

The pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD) open-label randomised trial was conducted at thirteen sexual health clinics in England and enrolled HIV-negative gay and other MSM who had had anal intercourse without a condom in the previous

ninety days end November 2012 to end April 2014. Among participants in the deferred group of these high risk men, HIV incidence was an estimated 9 per 100PY (90%CI 6·1-12·8).[29]

4.1.4. Recent HIV Infections

Several laboratory-based assays have been developed that can identify recent HIV infections through the testing of blood specimens. When interpreted as part of a Recent Infection Testing Algorithm (where laboratory test results are combined with other information to classify an HIV infection), these assays can distinguish recently acquired infection from long-standing infection among persons diagnosed with HIV. Although the scaled implementation of recency testing has been shown to be feasible, questions of utility and accuracy persist.[30-32] To date no recency assay has met the global target product profile for HIV incidence estimation.[33] Applying this method among adults attending sexual health clinics in England, it was estimated that HIV incidence remained stable between 2009 (1.24; 95%CI 0.96-1.52%) and 2013 (1.46%; 95%CI 1.23%-1.70%).[34]

Conclusions: Although it is difficult to compare all the presented estimates due to the differing methods and time periods applied, together they do suggest incidence now will be lower than 2014 GUMAD estimates, even when considering the recent slight increase in incidence suggested by CD4 back calculation. In accepting the estimate of 0·95 per 100PY based on non-PrEP Impact trial attendees as their preferred choice, the EAG noted that it was likely an underestimate of baseline risk for people who would receive cabotegravir as it relates to non-trial attendees who likely did not meet the high-risk enrolment criteria. We should note that the 2017-2020 estimate of 0.95 per 100PY is higher than the 2022/23 GUMCAD estimate of 0.43 per 100PY and the 2013-2019 clinic-based cohort of 0.71 per 100PY. For information, the Office for National Statistics estimated that in 2022, 986,000 (3.8%) of the UK male population identified as being gay or bisexual (a figure that will include people already living with HIV).[35]

The estimate of 0·95 per 100PY seems reasonable as a baseline for risk among MSM in the UK.

4.2. WHAT IS THE MOST PLAUSIBLE VALUE FOR BASELINE RISK CISGENDER WOMEN?

In their additional evidence, the UKHSA suggests that whilst there are no formal incidence estimates for all people exposed through sex between men and women, the rise in HIV diagnoses in this group, together with sustained test positivity and lower levels of HIV testing in sexual health services, suggest HIV transmission is not declining. In 2013, among heterosexual men and women (combined estimate) who had been newly diagnosed in the UK with HIV, and for whom a recency test result was available, an estimated 13% (80/660) had recently acquired their infection (an indication of incident infections).[24] Among MSM, the comparable figure was 30% (320/1080).[24] A

subsequent recency test-based analysis estimated HIV incidence among black African heterosexuals (men and women combined) to have increased, non-significantly, from 0.15% (95%CI 0.05%-0.26%) in 2009 to 0.19% (95%CI 0.04%-0.34%) in 2013.[34] These estimates were four to five-fold higher than among all heterosexuals among whom incidence was estimated to have remained stable (2009: 0.03%; 95%CI 0.02%-0.05%; 2013: 0.05%; 95%CI 0.03%-0.07%).[34]

The prevalence of HIV among black African men and women in the UK is elevated as compared to the population as a whole. Among adult participants of a cross-sectional community-based survey in London, Luton and the West Midlands in 2004, the majority of whom were born in southern or eastern Africa, 13% of black African men and 15% of black African women tested HIV positive.[36,37] To provide context to these estimates, shortly after this survey the Health Protection Agency recommended HIV testing services be expanded in Primary Care Trusts where the prevalence of diagnosed HIV exceeded 2 per 1,000 population (0.2%).[38] In 2023, an estimated 113,500 people were living with HIV in the UK among an estimated population of 68.35 million;[1,2,39] this provides a crude prevalence of 0.17%.

Conclusions: Although estimates for cisgender women we not available, the 2013 estimates of incidence among heterosexuals (0.05%) and black Africans (0.19%) are considerably lower than the 2013 MSM estimates presented above (1.46% and 1.47%). In 2014 (earliest year for which comparable data could be found), diagnoses among MSM exceeded those among heterosexuals (2,975 v 2,150, respectively), whereas in 2023 this had been reversed (1,377 v 3,579, respectively).[40] To note that, as highlighted above, a sizeable proportion of these "new" diagnoses are among people who were first diagnosed abroad. For information, according to the 2021 census, approximately 2.4 million people (4.2% of the total population) in England and Wales, identified as Black, Black British, Caribbean or African.[41]

It is probable that HIV incidence among cisgender women (based on estimates among all heterosexuals and black African heterosexuals) now exceeds the 2013 estimates but remains lower than the preferred estimate for MSM. Focusing on black African heterosexuals, and as informed by the information presented, we may suggest a very crude estimate of baseline risk of 0.5 per 100PY.

4.3. IN PRACTICE DOES THE BASELINE RISK OF HIV ACQUISITION DIFFER ACROSS SPECIFIC POPULATION GROUPS?

The company originally suggested risk among two populations be considered: people who cannot take oral PrEP because of medical contraindications or difficulty swallowing tablets, and people who do not take oral PrEP exactly as prescribed (including people unable to adhere to oral PrEP because of health-related or social difficulties and people whose needs were not met by oral

PrEP). The committee decided to only make recommendations for the whole population eligible for PrEP.

The National AIDS Trust have recommended that the committee considers adopting a scenario-based approach to baseline HIV incidence, rather than a single point estimate. They argue that a range of baseline incidence scenarios would better capture complexity and enhance the accuracy of a cost-effectiveness model.[42] They suggest the model could include a range of incidence values to reflect different high-risk subpopulations as well as markers of elevated risk such as condomless sex and sexualised drug use. In the UK 2018 PrEP guidelines, PrEP is recommended for those deemed to be high risk and to be considered for those categorised as medium risk.[43] High risk is defined as HIV-negative MSM and trans women who report condomless anal sex in the previous six months and on-going condomless anal sex and HIV-negative individuals having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. In terms of medium risk, PrEP may be offered on a case-by-case basis to HIV-negative individuals considered at increased risk of HIV acquisition through a combination of factors that may include population-level factors such as black African ethnicity or clinical indicators such as STIs. Oral PrEP guidance also consider indicators of diminished sexual health autonomy; for example women experiencing intimate partner violence.

Conclusions: Due to the absence of routinely available, timely, and robust data to inform sub-population specific differentiations relating to an ability to take oral PrEP, risk behaviours, and partner information, it may be pragmatic to proceed with baseline estimates for the two populations most at-risk and for whom estimates are available: namely, MSM (as a proxy for TGS) and black African heterosexuals (as a proxy for cisgender women).

4.4. SHOULD THE AT RISK PERIOD BE FIVE OR TEN YEARS?

Highlighting that there was no data available on the mean duration of the at-risk period for HIV acquisition, the company commented that an at-risk period for HIV acquisition of five years was appropriate. A clinical expert explained that there are multiple components that define HIV risk and most of them do not stay constant over time, so considered that five years is an appropriate estimate for the at-risk period of HIV acquisition. To account for uncertainties associated with using a single period for HIV risk and PrEP use, the EAG preferred to use an at-risk period for HIV acquisition of ten years. The committee noted there was uncertainty associated with using a single at-risk period for HIV acquisition in the model, so it was appropriate to use a conservative estimate of ten years for this assumption. The committee also noted that although real-world evidence showed high discontinuation of PrEP over 12 months, it was not clear how many people restart PrEP.

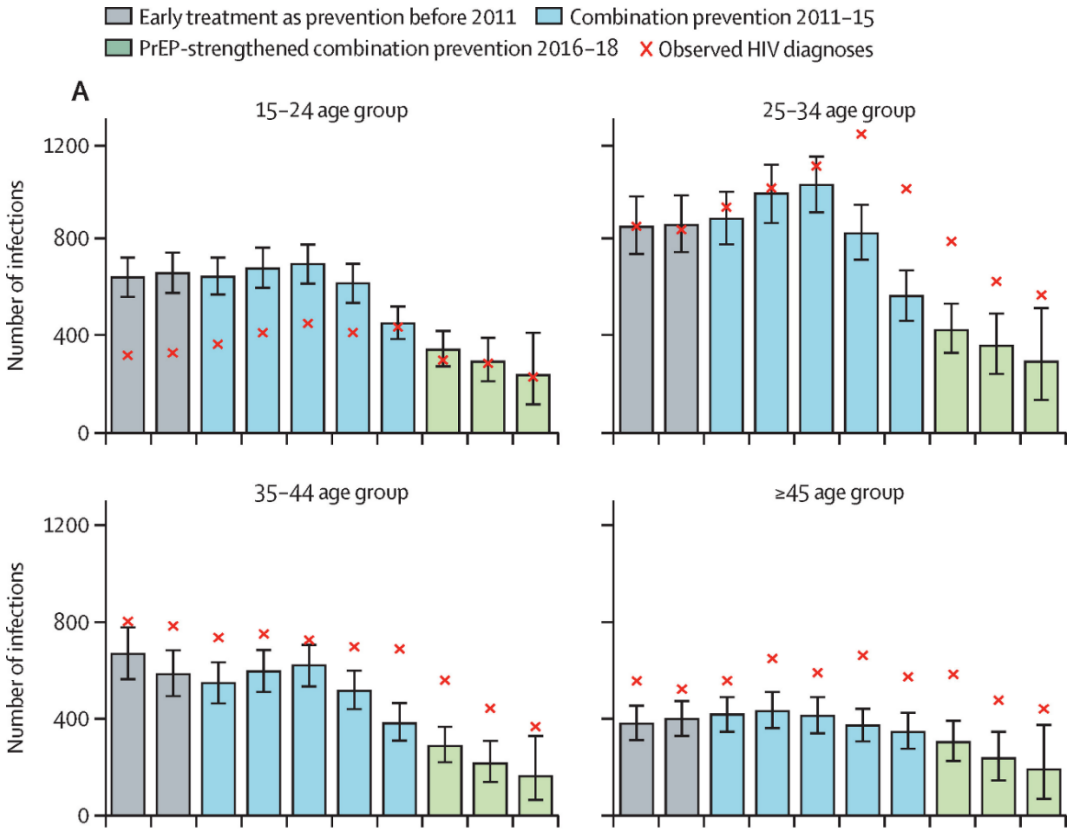
A 2024 systematic review and meta-analysis of PrEP restarting globally reported higher restarting in studies among heterosexual populations compared to MSM or transgender women (aOR 1.50; 95%CI 1.25-1.81) and in studies defining restarting as those who had stopped PrEP for >1 month compared to those who stopped <1 month (aOR 1.20; 95%CI 1.06-1.36).[44] Reasons for restarting PrEP included perceived higher risk for HIV acquisition and removal of barriers to access PrEP. The authors of the review report that about a quarter of people who stopped PrEP restarted, with substantial variation across countries and populations.[44] A 2022 global systematic review and meta-analysis of discontinuation, suboptimal adherence, and reinitiation of oral PrEP reported that among people who discontinued PrEP, nearly half (47·3%; 95%CI 31·5-63·2) reinitiated PrEP within one year of PrEP initiation.[45] The authors of the review note that as they included poor quality studies there was a moderate risk of bias.

Although age stratified incidence estimates do not indicate length of period at risk, they can explore whether risk is present across all age groups The age-stratified CD4-staged Bayesian back-calculation model among adult MSM in England 2009 to 2018 presented above, highlighted new infections across all age groups as well as the decline in estimated incidence being slowest among those aged ≥45 years (Figure 5).[25]

In a study analysing prevalence-based HIV incidence estimate among women who sell sex in Zimbabwe, researchers reported ongoing high incidence of infections among women who had been selling sex for between six and fifteen years (2.1 per 100PY).[18] Although these estimates are unlikely to be generalisable to a wider population, they do highlight ongoing risk among a high-risk group.

Conclusion: Of the two proposed options of five or ten years, the evidence appears to support the adoption of ten years.

Figure 5: Back-calculation age-stratified estimated annual number of new HIV infections among MSM in England 2009 to 2018 with associated 95% credible intervals



Crosses represent the observed annual number of new diagnoses.

5. CONCLUSIONS

This review reflects on four issues pertaining to baseline risk of HIV acquisition in the UK; our response to these issues are summarised below:

What is the most plausible value for baseline risk among MSM/TGW? We suggest the EAGs preferred estimate of 0·95 per 100PY is reasonable.

What is the most plausible value for baseline risk among cisgender women? Focusing on black African heterosexuals, we suggest a crude estimate of baseline risk of 0.5 per 100PY.

In practice does the baseline risk of HIV acquisition differ across specific population groups? The evidence suggests that baseline risk does differ across population groups and, therefore, we suggest proceeding with baseline estimates for MSM and black-African heterosexuals.

Should the at-risk period be five or ten years? We suggest proceeding with a ten-year at-risk period.

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Single Technology Appraisal

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

DSU report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by 5pm on 11th June 2025 using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Contents

Decision Support Unit (DSU) report

Issue 1 Use of data from populations that do not represent the decision problem population: people at high risk of HIV acquisition who are not on PrEP

Description of problem	Description of proposed amendment	Justification for amendment	DSU response
Page 1 The DSU state: *"and a 2019 MSM clinic-based cohort estimate of 0.25 per 100 person-years."* Page 14 The DSU state: *"The authors of this study reported a substantial decline in HIV incidence from 1.47 per*	Please remove this statement or add a more comprehensive description of the AURAH 2 study population.	The statistic does not reflect the intended population and is therefore not appropriate and misleading.	This study included HIV-negative GBMSM attending for STI or HIV tests at one of three large London or Brighton sexual health clinics (settings where the prevalence of HIV is elevated), a group at high risk of HIV-acquisition in the UK. The estimates from this study provide helpful context / comparators to

Description of problem	Description of proposed amendment	Justification for amendment	DSU response
100PY in 2013 to 0.25 per 100PY in 2019.[26]" These values do not reflect the intended population i.e. people at high risk of HIV acquisition not on PrEP. The data are from AURAH 2; the authors have published the proportion of PrEP use in the sample, with PrEP use among 78% of participants who reported condomless sex with two or more partners (1)			other similar incidence estimates under review. In response to comments, we have expanded our description of the methods and limitations of this study, as well as PrEP use among participants. We now focus on the overall estimate spanning 2013 to 2019 rather than the year specific estimates. We have amended p4 (executive summary), p15, and p16 accordingly.

Issue 2 Clarity and accuracy

Description of problem	Description of proposed amendment	Justification for amendment	DSU response
Page 1 The DSU state: *"this review highlights that it is higher than the 2022/23 Genitourinary Medicine Clinic Activity Dataset (GUMCAD) MSM estimate*	Please remove this statement.	Methods are not reported and so it cannot be confirmed whether this statement is accurate; therefore, use of this statistic is not appropriate.	On page 10 we highlight that "…the company recommended to ACM2 the adoption of a baseline incident rate of 3.9 per 100 person-years (PY) based on the Genitourinary Medicine

Description of problem	Description of proposed amendment	Justification for amendment	DSU response
of 0.43 per 100 person-years" It is not clear whether individuals using PrEP are included within this estimate, and whether this represents baseline risk or risk with some oral PrEP use, therefore this comparison may not be appropriate			Clinic Activity Dataset (GUMCAD) 2014 reported value for MSM who had a rectal bacterial Sexual Transmitted Infections (STI) and an HIV test in the past 12 months. The 2022/23 GUMCAD estimate applies the same methodology as that for 2014. These GUMCAD estimates provide helpful context / comparators to other incidence estimates under review (including the 2014 GUMCAD-based estimates). In response to comments, we have expanded our description of the GUMCAD methods and provide an additional reference that presents further information on this

Description of problem	Description of proposed amendment	Justification for amendment	DSU response
			surveillance platform. We have amended p13 accordingly.
Page 1 The DSU state: *"Those providing HIV services in the UK have also indicated that it is often challenging to assess risk"* Clinical experts identified at previous ACMs they are able to identify risk among people attending sexual health services.	Please remove this statement.	Clinicians consulted at previous advisory boards indicated that risk assessment is routinely done in clinical practice and follows clinical guidelines, but no challenges to identifying risk were reported.	In relation to the proposed amendment, it is suggested clinical experts have expressed their opinion that they are able to identify risk. There is a body of evidence highlighting numerous challenges to clinic-based risk assessment. These challenges include low risk perception among attendees leading to inaccurate reporting, attendees not disclosing risk behaviour due to fear and stigma, cultural and social factors that influence reporting of risk, and assumptions made by healthcare workers resulting in misclassified risk. Rather than further extend the report, we have focused on presenting

Description of problem	Description of proposed amendment	Justification for amendment	DSU response
			additional information to support our original argument that risk is challenging to assess in relation to place of infection (a major risk variable in the UK context and one that influences our estimates of new-diagnoses and incidence). On page 12, we clarify that in a review of UK HIV surveillance data (which Dr Rice led) HIV treatment clinic staff indicated that it was often unclear whether a person had acquired their infection in the UK or abroad due to complex sexual and migration histories spanning many years. We now present two studies highlighting how clinic-based assessment of risk underestimated UK-acquisition of HIV among African communities.

References

1. Hanum N, Cambiano V, Sewell J, Rodger AJ, Nwokolo N, Asboe D, et al. Trends in HIV incidence between 2013-2019 and association of baseline factors with subsequent incident HIV among gay, bisexual, and other men who have sex with men attending sexual health clinics in England: A prospective cohort study. PLoS Med. 2021;18(6):e1003677.