NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Cabotegravir for preventing HIV-1 in adults and young people

1 Recommendations

People who cannot have oral PrEP

1.1 Cabotegravir is recommended as an option for pre-exposure prophylaxis (PrEP) alongside safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults and young people at high risk of getting HIV and who weigh at least 35 kg, only if:

- they cannot have oral PrEP
- cabotegravir is purchased at the Medicines and Procurement Supply Chain framework price (see section 2).

People who can have oral PrEP

1.2 Cabotegravir is not recommended for PrEP alongside safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults and young people at high risk of getting HIV and who weigh at least 35 kg, if they can have oral PrEP.

About these recommendations

1.3 These recommendations are not intended to affect treatment with cabotegravir that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For young people, this

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decision should be made jointly by the healthcare professional, the young person and, when appropriate, their parents or carers.

Why the committee made these recommendations

People at high risk of getting HIV can reduce their risk by taking daily PrEP tablets (oral PrEP). But some people cannot have oral PrEP. Cabotegravir is a long-acting injection for PrEP that is used every 2 months.

Evidence from clinical trials and indirect comparisons suggests that cabotegravir reduces the risk of getting HIV more than oral PrEP or no PrEP.

The cost-effectiveness estimates for cabotegravir are only within the range that NICE considers an acceptable use of NHS resources when compared with no PrEP. So, cabotegravir is only recommended for reducing the risk of HIV-1 infection in people who cannot have oral PrEP.

2 Information about cabotegravir

Marketing authorisation indication

2.1 Cabotegravir (Apretude, ViiV Healthcare) is indicated 'in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for cabotegravir.

Price

2.3 The list price of cabotegravir is £1,197.02 for 1 vial of prolonged-release suspension for bimonthly injection and £638.57 for a 30-day pack of oral tablets (excluding VAT, BNF online accessed September 2025).

2.4 The company has a commercial arrangement. This makes cabotegravir available to the NHS with a discount via the Medicines Procurement and Supply Chain (MPSC) framework. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for ViiV Healthcare will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by ViiV Healthcare, a review of this submission by the external assessment group (EAG), an independent review from the Decision Support Unit (DSU), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 HIV is a retrovirus that infects and destroys immune cells that have a key role in fighting infections. The destruction of these cells leaves people living with HIV unable to fight off infections and some other conditions. It can result in complications from advanced HIV, also known as AIDS. There are 2 main types of HIV. Most cases within the UK are from the HIV-1 type, which is considered more transmissible than HIV-2. HIV is transmitted through bodily fluids of a person living with HIV who is not on effective treatment. This can be during sexual contact, by vertical transmission (during pregnancy, birth and breastfeeding), and by sharing equipment used to inject drugs.

Clinical management

3.2 Oral pre-exposure prophylaxis (PrEP) may be offered to people at higher risk of acquiring HIV (see NICE's guideline on reducing sexually transmitted infections). People at higher risk of acquiring HIV can be

identified using the criteria in the British HIV Association and British Association for Sexual Health and HIV guidelines on the use of HIV PrEP (PDF). Oral PrEP typically involves taking daily tablets, but in some cases it can be used before sexual exposure (event-based or on-demand PrEP). Most people using oral PrEP in the UK will have tenofovir disoproxil plus emtricitabine (TDF-FTC), which is considered standard care. Tenofovir alafenamide plus emtricitabine (TAF-FTC) can be offered as a second-line option when TDF-FTC is not tolerated or contraindicated. TAF-FTC is also only licensed for HIV PrEP in at-risk men who have sex with men (MSM), including young people. Although oral PrEP is effective, the community expert and clinical experts explained that there may not be full adherence for a variety of reasons, including psychosocial issues such as stigma or changes in lifestyle, difficulty swallowing tablets, difficulty accessing treatment and lack of awareness. The community expert noted that factors such as homelessness and domestic violence can make it difficult to take oral PrEP every day. They noted that a long-acting prevention option would make it easier to adhere to HIV PrEP in these situations. Both the community expert and clinical experts highlighted that a long-acting prevention option could increase the number of people using and adhering to HIV PrEP. The committee concluded that a long-acting PrEP will be a valuable option for some people.

Positioning of cabotegravir

3.3 The marketing authorisation for cabotegravir covers people at high risk of sexually acquired HIV-1 infection. But in its submission the company positioned cabotegravir for a narrower population, which included 2 separate populations of people at high risk of sexually acquired HIV1 infection:

- people who cannot take oral PrEP because of medical contraindications or difficulty swallowing tablets
- 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
- people whose needs were not met by oral PrEP

The company explained that people who take oral PrEP exactly as prescribed already have their PrEP needs met. The committee was aware that PrEP is often stopped and started. It was concerned that people who currently take oral PrEP exactly as prescribed may not continue to do so in the future, and could easily enter the subpopulation of 'suboptimal use'. The committee also noted 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. The committee was also aware that some people who take oral PrEP exactly as prescribed may also prefer to use cabotegravir rather than oral PrEP, and should not be omitted from the population for whom oral PrEP is an option. The committee concluded that it could not make a recommendation for only the subpopulation of people who cannot take oral PrEP or who do not take oral PrEP exactly as prescribed.

The committee then explored if it was possible to define a population of people who cannot have oral PrEP. The clinical experts explained that everyone visiting sexual health services (SHS) will have a risk assessment, and a very small proportion of people will need an alternative to oral PrEP. They also explained that there is a well-defined population for whom oral PrEP is not appropriate, which may include:

- people for whom oral PrEP is medically contraindicated
- people who cannot have oral PrEP tablets

- people who cannot have oral PrEP because of social or personal circumstances.

The clinical experts explained it is already possible to easily identify these people based on existing clinical knowledge. The committee acknowledged the unmet need for people who cannot have oral PrEP, and understood that it was possible to identify this population in clinical practice. It concluded that it would be able to make separate recommendations for the subpopulation of people who cannot have oral PrEP.

Comparators

People who cannot have oral PrEP

3.4 In its submission, the company presented comparisons with TDF-FTC and no PrEP. For people who cannot take oral PrEP, the company commented that no PrEP is an appropriate comparator. The committee noted that some people who cannot take oral PrEP will have contraindications for oral PrEP but not for cabotegravir. Because the committee had established that there was a population that cannot have oral PrEP (see section 3.3), it concluded that no PrEP should be considered a comparator for those who cannot have oral PrEP.

People who can have oral PrEP

3.5 For people who do not take oral PrEP exactly as prescribed, the company commented that oral PrEP and no PrEP were appropriate comparators. It noted that oral PrEP may not be appropriate for everyone who is eligible. This was shown in the clinical trial populations, in which some people did not take oral PrEP exactly as prescribed. The company noted that TAF-FTC has negligible use in clinical practice, so it only provided a comparison with TDF-FTC. The committee agreed that TDF-FTC was an appropriate comparator to represent oral PrEP. A clinical expert commented that no PrEP should also be considered a comparator in this population, because there are people in clinical practice who cannot or will

not take oral PrEP but have a PrEP need. The committee noted that those who do not have or adhere to oral PrEP for psychosocial or lifestyle reasons are difficult to define (see section 3.3), and that it is not clear if these groups would find cabotegravir an acceptable alternative to oral PrEP. The committee acknowledged that having the option of cabotegravir as PrEP could mitigate some of the psychosocial or lifestyle factors that cause people to not take PrEP exactly as prescribed. Because the committee had previously established that it was possible to define a population for people who cannot have oral PrEP (see section 3.3), it concluded that for the rest of the population eligible for cabotegravir who can have oral PrEP, oral PrEP (that is, TDF-FTC) is an appropriate comparator.

Clinical effectiveness

HPTN 083 and 084 trials

3.6 Clinical-effectiveness evidence for cabotegravir injections compared with TDF-FTC is from the HPTN 083 and HPTN 084 trials. HPTN 083 was a phase 2b and 3, double-blind randomised controlled trial (RCT) that included cis men and trans women who have sex with men and are at risk of acquiring HIV. The trial locations included sites across Latin American and South-East Asian countries, the US and South Africa. The company presented results from the primary analysis for the modified intention-to-treat population, which had a follow up of 153 weeks. Cabotegravir showed a statistically significant reduction in the number of HIV acquisitions compared with TDF-FTC (hazard ratio [HR] 0.34, 95% confidence interval [CI] 0.18 to 0.62). HPTN 084 was a phase 3, double-blind RCT that included cis women aged 18 to 45 at risk of acquiring HIV. The trial locations included sites across sub-Saharan African countries. The company presented results from the primary analysis for the modified intention-to-treat population, which had a follow up of 185 weeks. Cabotegravir showed a statistically significant reduction in the number of HIV acquisitions compared with TDF-FTC (HR 0.12, 95% CI 0.05 to 0.31;

p<0.0001). The committee concluded that cabotegravir reduced HIV acquisition compared with TDF-FTC. The EAG commented that neither of the HPTN trials was based in the UK, which introduced uncertainty about the generalisability of the results. A clinical expert explained that the trial data was generalisable to a UK population because the people in the trials were from groups who would also be at high risk of acquiring HIV in the UK. They noted that this was more important than the geographical locations of the trials in relation to generalisability. The committee concluded that the clinical trial results were the best available evidence and could be used for decision making.

Indirect treatment comparison

3.7 There was no direct comparison data between cabotegravir and no PrEP. So, the company did an indirect treatment comparison (ITC) informed by a systematic literature review. Results suggested that cabotegravir had a higher predicted effectiveness compared with no PrEP. The company considers the exact values confidential so they cannot be reported here. The company also used the ITC to describe the relationship between TDF-FTC effectiveness (compared with no PrEP) and adherence. This was based on a meta-regression that accounted for variation in TDF-FTC adherence between the studies included in the analysis. The company found a strong relationship between TDF-FTC adherence and effectiveness. The company considers the exact results to be confidential so they cannot be reported here. The ITC also allowed modelling of the baseline risk of HIV acquisition for those who do not have PrEP. The EAG was satisfied that the results were suitable for decision making. The committee concluded that the ITC results were acceptable for decision making.

Efficacy data from oral lead-in

3.8 The summary of product characteristics for cabotegravir allows for an optional oral lead-in (OLI) phase using cabotegravir tablets before having cabotegravir injections to assess tolerability. The initial company base

case assumed that 50% of people had this OLI. At the third committee meeting, the company updated its base case to assume that 0% of people had an OLI phase, and based its updated efficacy estimates on data from the injection phase only. It cited a US-based real-world evidence study (Hazra et al. 2024; poster presentation) in which 97.8% of people (n=270) having cabotegravir for PrEP did not have the OLI. It highlighted that the remaining proportion of people who did have the OLI would not be a significant driver of cost effectiveness. So the company thought it was appropriate to consider the efficacy of cabotegravir using data based on the injection phase only. The company also suggested that HIV acquisition risk during the OLI phase may be higher because of suboptimal adherence to oral PrEP. The EAG said that suboptimal adherence to oral PrEP may not be linked to all HIV acquisitions and that excluding people in the OLI phase may bias the analysis. The committee thought that it was plausible that most people may not have the OLI in clinical practice. But it noted that because the OLI phase is used to assess tolerability, changes to the proportion of people having the OLI would also lead to a change in the proportion of adverse events and the costs associated with these. But these changes to adverse events were not included in the company's updated base case. So the committee concluded that it was appropriate to use the efficacy data with an assumed OLI phase for 50% of people in decision making. But, it acknowledged that the proportion of people having this may be lower in clinical practice.

Economic model

Company's modelling approach

3.9 The company used a Markov model, including the impact of HIV infections and of future HIV infections caused by the initial HIV acquisition. The model had a cycle length of 1 month and a lifetime time horizon. It consisted of 5 health states: on cabotegravir, on TDF-FTC, not taking PrEP, living with HIV, and death. The model assumed an aggregate risk

period of 5 years within which people are at risk of HIV. Afterwards, people are assumed to no longer be at risk of HIV. The model used a single risk period to represent the lifetime risk duration for people eligible for PrEP. The company acknowledged that this was a simplified approach, but that attempting to model multiple risk periods would have been very complex and would not have improved the clinical validity of the model structure to the decision problem. The EAG commented that the company's model structure appropriately captured the decision problem. The committee concluded that the economic model structure was acceptable for decision making.

Baseline risk of HIV acquisition for MSM and trans women

3.10 Baseline risk of HIV acquisition, that is the incidence of HIV in a population, was a significant driver of cost-effectiveness estimates in this appraisal. This was because differences in baseline risk affect the number of HIV cases in the population and changes the number of cases prevented by existing PrEP options. In the modelling for this appraisal, a higher baseline risk of acquisition resulted in lower cost-effectiveness estimates for cabotegravir, and vice versa. The company's initial model used a value of 4.9 per 100 person-years, but after draft guidance consultation, the company's revised model used a baseline value for HIV acquisition of 3.9 per 100 person-years. This was based on the value reported in the Genitourinary Medicine Clinic Activity Dataset (GUMCAD) for MSM who had a rectal bacterial sexually transmitted infection (STI) and an HIV test in the past 12 months. In its response to draft guidance, the UK Health Security Agency (UKHSA) noted that the company's baseline value for HIV acquisition was based on data from 2014. Modelling evidence calibrated to UKHSA data estimated that HIV incidence among MSM declined significantly between 2014 and 2023. The UKHSA commented that the PrEP Impact Trial assessed HIV incidence among attendees at SHS in England between 2017 and 2020 (Sullivan et al. 2023). The trial reported an incidence of 0.95 per 100 person-years for the overall population of MSM attendees at SHS

who tested negative for HIV and did not participate in the trial. Given the scale and design of the trial, the UKHSA considered this to be a robust estimate of current incidence rates among MSM attending SHS. The EAG agreed that 0.95 per 100 person-years was an appropriate value for baseline risk of HIV acquisition, but acknowledged this was highly uncertain.

Ahead of the third committee meeting, additional evidence on baseline risk of HIV acquisition was requested, and was reviewed by the DSU. The DSU explained that after carrying out an independent analysis based on the existing evidence, it supported an estimate of 0.95 per 100 person-years for baseline risk of HIV acquisition in MSM, and as a proxy figure for trans women. It explained that since 2014 there has been a marked decline in HIV acquisitions across the UK, probably because of increased use of antiretrovirals, the introduction of PrEP and more widespread testing for HIV. The clinical experts highlighted that the HIV incidence value from the PrEP Impact Trial was based on those attending SHS only. This does not capture populations with a PrEP need that typically do not engage with SHS. These underserved populations would probably benefit most from cabotegravir if it were recommended as an option for PrEP. The clinical experts also noted that the baseline incidence value of 0.95 per 100 person-years was based on non-trial attendees. Participants in the PrEP Impact Trial were recognised to be at high risk for HIV, so non-trial attendees probably did not meet this criterion. The marketing authorisation for cabotegravir covers people at high risk of sexually acquired HIV. So, they considered that the value for the baseline risk of HIV acquisition would probably be higher than 0.95 per 100 person-years for those eligible for cabotegravir. The company highlighted the latest GUMCAD analysis from the UKHSA. This showed that, in MSM attending SHS services who were not on PrEP and who had a recent rectal bacterial STI in the previous year, the incidence rate in 2022 to 2023 was 1.9 per 100 person-years (95% CI 1.13 to 3.21 per 100 person-years).

The company thought that this was still an underestimate because it did not take into account other markers of high risk of acquisition. It explained that the GUMCAD analysis may not account for exposure to oral PrEP during the observed follow up. But, it thought that it was still reasonable to consider this estimate along with the 3.9 per 100 person-years estimate in its base case. The company also highlighted recent stakeholder comments submitted ahead of the third committee meeting, suggesting ranges of 2 to 3 per 100 person-years and 3.9 to 9 per 100 person-years for HIV acquisition. The clinical experts explained that it is possible for people to access oral PrEP at a different centre from where they may have diagnosis and treatment of STIs, which may not be captured in the GUMCAD analysis. The UKHSA explained that the updated analysis from GUMCAD replicated the legacy method from 2014, using the most recent surveillance data from GUMCAD. But it also highlighted that the analysis could not be generalised to all MSM because they may not be engaging with these services. It thought that the estimate of 1.9 per 100 person-years for people not on PrEP may be reasonable. The committee understood that HIV incidence was likely to have substantially decreased since 2014, and that data from 2014 was unlikely to be representative of the current baseline risk. The committee noted that the range of more recent estimates of baseline risk was much lower, and considered the range of more recent values it had been presented with. It also acknowledged the challenges of generating evidence on baseline risk. It acknowledged that the experts viewed 1.9 per 100 person-years as an underestimate of baseline risk of HIV acquisition in MSM and trans women and that this may be higher in clinical practice. It also noted that it had seen lower values and acknowledged the uncertainty around data for baseline risk. The committee concluded that, on balance, it was appropriate to use a baseline HIV acquisition risk of 1.9 per 100 person-years in MSM and trans women in its decision making.

Baseline risk of HIV acquisition for cis women

3.11 The company's economic model assumed that 3.2% of the population being considered in this appraisal are cis women. For this population, it assumed a different baseline HIV acquisition risk from that for the MSM and trans women population. The EAG preferred a different risk level for baseline HIV acquisition in cis women (these estimates are confidential and cannot be reported here). Stakeholder comments submitted ahead of the third committee meeting highlighted that a recent Africa-based RCT of women using oral PrEP (PURPOSE-1) reported a background HIV incidence of 2.41 per 100 person-years. They also highlighted that the UK-based data for cis women was extremely limited and PURPOSE-1 data may be generalisable to the UK because HIV disproportionately affects heterosexual men and women of African origin. The DSU explained that HIV prevalence in African communities in parts of the UK may not be dissimilar to prevalence in sub-Saharan Africa, but that this does not equate to incidence. It also explained that these estimates may not be generalisable because HIV acquisition is driven by increased prevalence of early infection, which is lower in the UK, as well as sustained viral suppression, which is likely to be higher in the UK. It suggested a crude estimate of 0.5 per 100 person-years in this population. The committee acknowledged that the data available for this population was extremely limited. It noted that it was less of a driver of cost effectiveness than the baseline risk for MSM and trans women. But it thought that, on balance, and given the preferred estimate for MSM and trans women of 1.9 per 100 person-years (see section 3.10), the EAG's preferred estimate of baseline risk for cis women was more appropriate for decision making.

Duration of HIV risk period

3.12 The company's economic model assumed a single period of HIV risk and PrEP use over a person's lifetime. The company acknowledged that a person's level of HIV risk will change throughout their lifetime and that PrEP is mostly used over multiple short-term periods. The company commented that an at-risk period for HIV acquisition of 5 years was

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appropriate. It explained that there was no data available on the mean duration of the at-risk period for HIV acquisition. But real-world evidence showed high rates of PrEP discontinuation (over 40% at 12 months). The company commented that this suggested that the mean at-risk duration may be shorter than 5 years and is unlikely to be longer. The EAG agreed that people eligible for PrEP have multiple short-term engagements with PrEP over their lifetime. 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 10 years. It also noted that using a shorter 5-year risk period capped the costs of cabotegravir and oral PrEP for the same amount of time, which favours cabotegravir. The DSU explained that recent data in the literature supports consistent restarting of oral PrEP and that ongoing risk may persist in high-risk groups. It thought that, on balance, a 10-year risk period was more appropriate than 5 years. A clinical expert explained that there are multiple factors that define HIV risk and most of them do not stay constant over time. So they considered that 5 years is a more appropriate estimate for the at-risk period of HIV acquisition. They also agreed that most people use PrEP over multiple short-term periods. The committee noted that the company's proposed positioning was for people at high risk of HIV. Some people may have oral PrEP over multiple short-term periods for a cumulative period of longer than 5 or 10 years, or for a prolonged period, if they are still at high risk of HIV exposure. The committee thought that the risk period may have a wide distribution based on individual risk. It also noted that although real-world evidence showed high discontinuation over 12 months, it was not clear how many people would restart PrEP. The committee noted there was uncertainty associated with using a single at-risk period for HIV acquisition in the model. The committee thought that a risk period of up to 10 years could be plausible, or longer in some groups. But, on balance, the committee concluded that it was appropriate to model a 5-year at-risk period for HIV acquisition for the population as a whole.

Transitioning from cabotegravir to TDF-FTC

3.13 The company's economic model allowed people in the cabotegravir arm who do and do not take oral PrEP exactly as prescribed to transition to TDF-FTC after stopping cabotegravir. The company explained that this was in line with the cabotegravir summary of product characteristics, which recommends alternative non-long-acting forms of PrEP in the months after stopping cabotegravir. In the company's cost-effectiveness analysis, 50% of people transitioned to TDF-FTC. The company also applied a high monthly TDF-FTC discontinuation rate to those who transitioned from the cabotegravir arm. The company considers the exact discontinuation rate to be confidential, so it cannot be reported here. The EAG commented that it is not logical for people in the cabotegravir arm to transition to oral PrEP if it was not appropriate for them. It also noted that a similar assumption was not made for people in the oral TDF-FTC arm transitioning to cabotegravir, which favours cabotegravir. The committee noted that it would not expect people in the oral TDF-FTC arm to transition to the cabotegravir arm because cabotegravir is not currently used in clinical practice. A clinical expert explained because the evaluation population included people who do and do not take oral PrEP exactly as prescribed, oral PrEP would be appropriate for a proportion of these individuals. They also noted that most people who prefer cabotegravir injections over oral PrEP would still take oral PrEP if it were the only option. For these reasons, the experts commented that allowing a proportion of people in the cabotegravir arm to transition to TDF-FTC after stopping cabotegravir would be appropriate and that the company's suggested proportion was reasonable. Additional evidence from stakeholders submitted ahead of the third committee meeting suggested that there would be limited transitions between cabotegravir and oral PrEP, at clinical discretion. The committee acknowledged that although there may be some transitioning from cabotegravir to oral PrEP, it was unlikely to be as high as the proportion suggested by the company. It concluded that, on balance, assuming no transition between cabotegravir and oral PrEP was sufficient for decision making.

Improved persistence with cabotegravir

3.14 Persistence refers to a person's willingness to continue taking a prescribed treatment for a given length of time. The company assumed that there would be a 20% improvement in persistence for people who have cabotegravir compared with oral PrEP. The company calculated discontinuation probabilities for oral PrEP. These were based on a US study that reported oral PrEP persistence at 6 and 12 months, and an international systematic literature review that reported discontinuation rates of oral PrEP within 6 months of starting treatment. The monthly discontinuation probability for oral PrEP was 5.73% over the first 6 months and 3.30% from 6 to 12 months. The company calculated the discontinuation probabilities for cabotegravir at 6 and 12 months, based on a US cost-effectiveness analysis of cabotegravir. The monthly discontinuation probability for cabotegravir was calculated as 2.82% over the first 6 months and 3.30% from 6 to 12 months. The company commented that the lower discontinuation probability for cabotegravir compared with oral PrEP at 6 months supported the 20% improvement in cabotegravir persistence assumed in the company model. The company also noted that 2 US-based real-world studies showed cabotegravir persistence to be 93% and 94%. In its response to draft guidance consultation, the company highlighted new real-world evidence from 15 clinics in the US showing cabotegravir persistence of 84.8% (95% CI 80.9 to 88.9%) for the first 6 months. As part of new evidence submitted ahead of the third committee meeting, the company did a new scenario analysis based on additional data (the source of the data is confidential so cannot be reported here). It also cited further real-world evidence from 6 US-based studies and 1 Brazil-based study, with a maximum follow up of 60 weeks, which supported high levels of persistence with cabotegravir. At the third committee meeting, it explained that the existing persistence data showed a 60% to 70% improvement for cabotegravir over oral PrEP, and that a 20% improvement in persistence assumed in the model was conservative. The company's clinical experts had also commented that a

20% improvement in persistence with cabotegravir compared with oral PrEP was a reasonable assumption. Ahead of the third committee meeting, stakeholders also commented that evidence from the literature shows that a long-acting injectable PrEP would increase PrEP uptake and persistence. The EAG preferred to assume that persistence with cabotegravir was equal to persistence with oral PrEP. It commented that there was no evidence directly comparing cabotegravir persistence with oral PrEP persistence. The EAG also noted limitations with the company's real-world studies, including the length of follow up, definition of discontinuation and the company's interpretation of persistence. The clinical experts commented that they expected persistence to improve with cabotegravir compared with oral PrEP. They explained that healthcare professionals administering cabotegravir would have procedures in place to ensure people having treatment are recalled for injections, and those who miss appointments are supported. 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 this data used. The committee thought that persistence may have been conflated with adherence, and noted that improvements in adherence for cabotegravir were already captured in the efficacy data. It considered analysis based on both assumptions and concluded that it was sufficient to assume that persistence with cabotegravir was equal to persistence with oral PrEP, but it acknowledged the uncertainty in this assumption.

Adherence to TDF-FTC

3.15 Adherence refers to the extent to which the person takes a medicine as agreed with their prescriber. In the company's model it was assumed that adherence to TDF-FTC was lower for cis women than for MSM and trans women. The company noted that clinical opinion, published literature and data from HPTN 084 supported this assumption. The clinical experts and the community expert both explained that cis women are less engaged with PrEP services in the UK. The EAG noted that the company did not

provide any evidence that was generalisable to a UK setting, so it preferred to assume that adherence to TDF-FTC was equal among cis women, trans women and MSM. The committee thought that even though the evidence highlighted by the company was not from UK-based studies, it was generalisable to UK clinical practice. The committee concluded that it was appropriate to assume that adherence to TDF-FTC was lower for cis women than for MSM and trans women.

Starting age of people in the model

3.16 The company assumed that the starting ages in the model were 31 years for MSM and trans women, and 29 years for cis women. This was based on UKHSA data that showed the median age of these populations accessing oral PrEP was between 25 and 34 years. The EAG noted that the model population is restricted to people at high risk of HIV acquisition. It commented that UKHSA data showed that those with the highest PrEP need were gay, bisexual and other men who have sex with men (GBMSM) aged 35 to 49. So the median age of people using PrEP in the model population is likely to be higher than that assumed by the company. The EAG preferred a starting age of 33, which is the approximate median age of people using PrEP in the UK, according to a cross-sectional study (Ogaz et al. 2022). The EAG believed this was a conservative estimate. The committee was aware that the starting age of people in the model had a relatively small impact on the cost-effectiveness estimates. It noted that the EAG's preferred starting age was towards the upper end of the range for MSM, trans women and cis women accessing oral PrEP (25 to 34 years), according to UKHSA data. So the committee concluded that a starting age of 33 was appropriate to use in the model.

Cabotegravir administration costs

3.17 In the company's model it was assumed that administration of cabotegravir injections would need 2 30-minute initiation injection appointments, with 20-minute appointments for subsequent injections. The administration costs were calculated according to these timings. The

company noted that a UK multicentre service evaluation of cabotegravir and rilpivirine pathways showed that appointments took 30 to 60 minutes and 40 minutes or less in 78% of NHS HIV clinics. The EAG commented that it was not appropriate for the company to assume that appointments for subsequent injections would take only 20 minutes. This was because evidence showed that appointments for cabotegravir and rilpivirine injections took longer than this (30 to 60 minutes). The EAG preferred to assume that all appointments for cabotegravir injections would take 1 hour of clinic time (20 minutes of a band 5 nurse for observation, 40 minutes of clinical activity). 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 person having PrEP may also need a review and they may have questions about PrEP, which would also take extra time. The committee concluded that cabotegravir administration costs should be based on 1 hour of clinic time.

Cabotegravir dosing schedule

3.18 In the company's model it was assumed that cabotegravir would be administered every 2 months after initiation injections, in line with the summary of product characteristics. The EAG commented that in the HPTN trials, cabotegravir was administered every 8 weeks. The EAG noted that even though the difference in time between 2 months and 8 weeks is small, using an 8-weekly dosing schedule increased the cost-effectiveness estimates. The clinical experts commented that most healthcare professionals would be confident administering cabotegravir every 2 months in clinical practice. The committee concluded that a dosing schedule of every 2 months was appropriate to use in the model. The EAG also commented that the company's model did not explicitly represent stopping and restarting PrEP over a person's lifetime. This meant that the costs of stopping and restarting PrEP are not captured in the model. The EAG proposed that a 5% increase should be applied to cabotegravir acquisition and administration costs, to account for discrepancy in the frequency of administration and stopping and restarting

of PrEP over the lifetime of the model cohort. The company commented that modelling increased costs and benefits of cabotegravir throughout multiple single time periods of PrEP use is unlikely to considerably impact the cost-effectiveness estimates. The committee acknowledged that stopping and restarting PrEP may incur additional costs. But it was not convinced that adding a 5% increase to cabotegravir acquisition costs was an appropriate way to capture them. The committee was also unsure why the increase should be applied only to the cabotegravir acquisition costs and not to TDF-FTC. The committee concluded that it was not appropriate to apply a 5% increase to cabotegravir acquisition and administration costs.

Rate of discontinuation

3.19 After the first committee meeting, the company amended the discontinuation rates of oral PrEP and cabotegravir in the model. It explained that the update was because of an implementation error and that the discontinuation rates had been applied for 5 monthly cycles instead of 6. The EAG explained that the company did apply discontinuation rates for 6 monthly cycles in the first implementation of the model and the updated version incorrectly applied this for 7 monthly cycles. The committee concluded that the initial method for applying discontinuation rates in the model was appropriate for decision making.

Utility values

Disutility of living with HIV

3.20 No health-related quality-of-life data was collected in HPTN 083 and HPTN 084. The company assumed that a disutility of -0.11 was associated with living with HIV, as was reported in Miners et al. (2014). The company noted that this value was selected based on study size, relevance to the UK population and the instrument used to measure health-related quality of life (EQ-5D-3L). The EAG commented that there have been improvements in anti-HIV treatments with fewer side effects

and less pill burden (the number of tablets a person has to take) since Miners et al. was published. The EAG preferred to use a disutility value of -0.05 reported in the Positive Voices Survey 2022. It noted that this more recent publication would capture the improvements in anti-HIV treatments. A community expert explained that there can be considerable stigma associated with HIV diagnosis, particularly among populations with poor awareness of HIV. The community expert noted that living with HIV can have devastating effects on a person's life, relationships and general wellbeing. The committee commented that both the company's and the EAG's preferred disutility values for living with HIV were plausible. It noted that there were limitations with both the company's and the EAG's evidence sources and that the most appropriate disutility value could lie between the company's and the EAG's preferred values. In the absence of further evidence, the committee commented that the most likely disutility value was probably closer to the company's value. So it concluded that a disutility value of -0.11 was most appropriate for decision making.

Implementation of cabotegravir injections

3.21 PrEP is currently administered in level 3 SHS. Both the clinical experts and commissioning experts expected that cabotegravir for PrEP would also be administered in level 3 SHS. The clinical experts noted that it would be useful if there were more routes available for people who need PrEP to access cabotegravir, for example GP surgeries or pharmacies. This could improve access for populations who typically do not engage with SHS for reasons such as stigma. A commissioning expert noted that there is a large demand for PrEP across the UK. Implementation of cabotegravir as an option for PrEP could result in considerable opportunity costs for existing SHS that already face funding constraints. The committee acknowledged the importance of ensuring those who need PrEP have adequate access to any new PrEP options, but noted that it was beyond the committee's remit to make any recommendations about implementation of PrEP services.

Severity

3.22 NICE's methods on conditions with a high degree of severity did not apply.

Cost-effectiveness estimates

Acceptable ICER

3.23 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects, including uncaptured health benefits. The committee noted several uncertainties, specifically:

- the appropriate value for risk of baseline HIV acquisition (see sections 3.10 and 3.11)
- the appropriate duration of the HIV risk period (see section 3.12)
- the proportion of people who should transition to TDF-FTC after stopping cabotegravir (see section 3.13)
- the percentage improvement in persistence that should be applied to people having cabotegravir (see section 3.14).

The committee also noted a high level of uncertainty around whether underserved populations would engage with SHS to access cabotegravir if it were recommended as an option for PrEP. But it also acknowledged the level of unmet need and the potential impact of health inequalities (see section 3.26). So, on balance, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

The committee's preferences and cost-effectiveness estimates

3.24 The cost-effectiveness estimates used by the committee for decision making took into account all of the available confidential discounts, including those for comparators. The exact estimates are confidential and cannot be reported here. The committee noted that the company's and the EAG's base cases differed on several assumptions. The company's base case at the third committee meeting showed that cabotegravir was dominant (that is, it was less expensive and more effective) when compared with both TDF-FTC and no PrEP. The EAG's base-case ICER at the third committee meeting was above £30,000 per QALY gained when compared with TDF-FTC and no PrEP. This reflected higher total costs of cabotegravir with relatively small modelled QALY gains. The committee preferred the model to include:

- efficacy estimates based on data with an assumed OLI phase for 50% of people (see section 3.8)
- an HIV baseline risk of 1.9 per 100 person-years for MSM and trans women (see section 3.10)
- an HIV baseline risk for cis women in line with the EAG's preference (see section 3.11)
- an HIV risk period of 5 years (see section 3.12)
- no transitioning between cabotegravir and oral PrEP (see section 3.13)
- no improvement in persistence for cabotegravir compared with oral PrEP (see section 3.14)
- lower adherence to TDF-FTC for cis women than for MSM and trans women (see section 3.15)
- a starting age of 33 years (see section 3.16)
- cabotegravir administration costs based on 1 hour of clinic time (see section 3.17)
- cabotegravir administration every 2 months (see section 3.18)
- application of discontinuation rates in the model as per the company's original approach (see section 3.19)

- a disutility of -0.11 associated with living with HIV (see section 3.20).

With the committee's preferred assumptions, cabotegravir was dominant compared with no PrEP, but the ICER was above the range NICE considers a cost-effective use of NHS resources when compared with TDF-FTC. So, the committee concluded that cabotegravir could be recommended for people who cannot have oral PrEP (the group for whom no PrEP is a relevant comparator).

Other factors

Managed access

3.25 Having concluded that cabotegravir could not be recommended for routine use outside of the population who cannot have oral PrEP, the committee considered whether it could be recommended for use during a managed access period. The committee questioned whether this could address uncertainties surrounding:

- baseline risk of HIV acquisition
- improvements in persistence with cabotegravir compared with oral PrEP
- whether populations with a PrEP need who are not currently engaging with SHS would access cabotegravir if it were available in practice.

The company did not make a proposal for managed access, and the committee acknowledged the difficulty in collecting this evidence. So, the committee was unable to consider a recommendation with managed access.

Equality

3.26 The committee recognised that some people at high risk of HIV may be people with Black African ethnic backgrounds and people with certain sexual orientations, such as gay or bisexual men. A clinical expert highlighted a considerable rise in HIV diagnoses for people with Black

African ethnic backgrounds between 2022 and 2023. The committee was aware that TAF-FTC is only licensed for HIV PrEP in at-risk MSM. So there is no licensed second-line option for other populations with a PrEP need when TDF-FTC is contraindicated or not tolerated. New evidence submitted ahead of the third committee meeting highlighted that people who may benefit from cabotegravir when current PrEP options are not appropriate may have protected characteristics, such as cis women and trans and non-binary people. Other underserved groups highlighted ahead of the third committee meeting included people who:

- inject drugs
- struggle with adherence or oral medicines
- have contraindications to current standard care PrEP
- are experiencing homelessness or are in unstable housing
- are experiencing intimate partner violence.

Key populations most at risk of HIV acquisition may be reluctant to engage in healthcare systems or to access SHS because of cultural concerns. Race, sexual orientation, sex, gender reassignment, and religion or belief are protected characteristics under the Equality Act 2010. The committee noted that issues related to differences in prevalence or incidence of a condition cannot be addressed in this technology appraisal. It could not directly address issues relating to engagement in healthcare systems or services. The committee recognised that the optimised recommendation permits only some of the potentially eligible population to access cabotegravir, but considered that this was justified because of the cost-effectiveness of cabotegravir in the different subpopulations. The committee acknowledged that cabotegravir may be beneficial for some disadvantaged groups, some of which have protected characteristics. So it took these potential equality issues into account in its decision making (see section 3.24).

Uncaptured benefits

3.27 The committee considered whether there were any uncaptured benefits of cabotegravir. It did not identify additional benefits of cabotegravir not captured in the economic modelling. So, the committee concluded that all additional benefits of cabotegravir had already been taken into account.

Conclusion

Recommendation

3.28 The committee concluded that cabotegravir may provide benefit in preventing HIV-1 infection, and acknowledged the high unmet need for groups underserved by oral PrEP. It acknowledged the high levels of uncertainty in the expected levels of engagement with SHS in these underserved populations if cabotegravir was recommended. It also thought that there was significant uncertainty around baseline risk of HIV acquisition, rates of transition between cabotegravir and oral PrEP, and persistence improvement with cabotegravir. With the preferred committee assumptions, the cost-effectiveness estimates for cabotegravir were within the range NICE considers a cost-effective use of NHS resources only when compared with no PrEP. So cabotegravir is recommended for reducing the risk of HIV-1 infection in people who cannot have oral PrEP.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or

treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person is eligible to have cabotegravir to prevent sexually acquired HIV-1 infection and the healthcare professional responsible for their care thinks that **Error! Reference source not found.** is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

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