NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Cabotegravir for preventing HIV-1

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using cabotegravir in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation 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 recommendations sound and a suitable basis for guidance to the NHS?
- 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?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using cabotegravir in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 17 October 2024
- Second evaluation committee meeting: 5 November 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 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.

1.2 This recommendation is 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 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

PrEP are medicines that people who have a higher risk of HIV can take to prevent them getting HIV. This involves taking tablets every day (oral PrEP). But some people cannot have or tolerate oral PrEP, and there are no other options available (no PrEP). Cabotegravir is a long-acting injection for PrEP that is used every 2 months.

Evidence from clinical trials shows that cabotegravir reduces the risk of HIV infection compared with oral PrEP. Cabotegravir has not been directly compared in a clinical trial with no PrEP. An indirect comparison suggests that it is more effective compared with no PrEP.

There are difficulties in determining who would have cabotegravir in NHS clinical practice and how to identify people who cannot have or tolerate oral PrEP. There are also uncertainties about how the clinical evidence applies to these populations.

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. So cabotegravir is not recommended.

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 proposed list price of 1 vial of prolonged-release suspension for injection and for a 30-day pack of oral tablets is commercial in confidence and cannot be reported here.

2.4 The company has a commercial arrangement. This makes cabotegravir available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by ViiV Healthcare, a review of this submission by the external assessment group (EAG), 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 (BHIVA and BASHH) 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 HIV1 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 in the future, and could easily enter the subpopulation of 'sub-optimal 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 people who take oral PrEP exactly as prescribed may also prefer to use cabotegravir rather than oral PrEP, and should not be excluded from the population under consideration. The committee concluded that it could not make a recommendation only for the subpopulation of people who cannot take oral PrEP or who do not take oral PrEP exactly as described. The EAG commented that people who cannot take oral PrEP were not included in the key

clinical trials. So the populations in the clinical evidence did not align with the populations covered by the company's proposed positioning of cabotegravir. The committee noted that everyone in the clinical trials had oral TDF/FTC or an oral placebo. So 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 population. The committee commented that the clinical trial populations would have included people who took oral PrEP exactly as prescribed, as well as those who did not. The committee acknowledged the difficulties defining the subpopulation of people who do not take oral PrEP exactly as prescribed, and uncertainty about whether the cost-effectiveness results were applicable to the evaluation population. For these reasons, the committee concluded that it could only make recommendations within the full marketing authorisation for cabotegravir. So further analysis using the whole population eligible for PrEP is necessary for the committee to make recommendations.

Comparators

People who cannot take 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. But, the EAG did not agree that no PrEP was an appropriate comparator for this evaluation. It commented that the populations in the clinical trials did not align with people who cannot take oral PrEP (see section 3.3). So there is no clinical trial data available to compare cabotegravir with no PrEP. The committee noted that some people who cannot take oral PrEP will have contraindications for oral PrEP but not for cabotegravir. So it concluded that no PrEP should be considered a comparator for those who cannot

take oral PrEP because of contraindications or difficulties swallowing pills. But it noted there was uncertainty around whether it was possible to make this comparison from the evidence submitted for the evaluation.

People who do and do not take oral PrEP exactly as prescribed

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. It also noted that the clinical trial included people who took PrEP exactly as prescribed, and that it was unclear if the analysis included only those who did not take oral PrEP exactly as prescribed. 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. The committee concluded that no PrEP and oral PrEP are appropriate comparators for people not taking oral PrEP exactly as prescribed. But, it was difficult to define the population these comparators would apply to and to determine which clinical trial evidence was relevant to this group. The committee also recalled that people who take oral PrEP exactly as prescribed may also prefer to use cabotegravir rather than oral PrEP, and considered that this group should be included. The committee concluded that further analysis

for the appropriate comparators using the whole population eligible for PrEP was necessary for decision making.

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 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, randomised controlled trial 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 were 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 HIV acquisition 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 showed that cabotegravir had a higher predicted effectiveness compared with no PrEP. The company considers the exact values confidential so they could not 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 could not be reported here. The ITC also allowed modelling of the baseline risk of HIV acquisition for those who do not have PrEP. The EAG noted some methodological issues with the company's ITC which introduced uncertainty, but it was satisfied that the results were suitable for decision making. The committee concluded that the ITC results were acceptable for decision making.

Economic model

Company's modelling approach

3.8 The company used a Markov model, including the impact of HIV infections and also 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

3.9 In the company model, a baseline value for HIV acquisition of 4.9 per 100 person-years was used. 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) in the previous year. The company noted that this value was also similar to the estimated background risk of HIV acquisition from the ITC for the HPTN 083 population of MSM (the company considers the exact value to be confidential so it could not be reported here). The EAG noted that the company's estimate for baseline risk of HIV acquisition was biased by potential inclusion of people who may have already been diagnosed with HIV outside of the UK. It noted that 36% of new HIV diagnoses in England in 2022 were for those previously diagnosed abroad. The EAG preferred to use a baseline value for HIV acquisition of 3.9 per 100 person-years. This was based on the GUMCAD-reported value for MSM who had a rectal bacterial STI and an HIV test in the past 12 months. The EAG noted that using this estimate for the population removed the potential inclusion of those who may have HIV at the time of testing. A clinical expert agreed that using a baseline HIV acquisition estimate for MSM was most appropriate, because this population is tested most frequently, so the data is most reliable. They commented that 4.9 per 100 person-years was the more appropriate value to use because only a small minority of people who were previously diagnosed will contribute to this estimate. The committee acknowledged that there were limitations with both the company's and EAG's preferred values for the baseline risk of HIV acquisition. The committee noted that there was uncertainty around the potential inclusion of people who may already have HIV in the 4.9 per 100 person-years estimate. Because of this uncertainty, the committee

concluded that it preferred the more conservative estimate of 3.9 per 100 person-years for baseline HIV acquisition.

Duration of HIV risk period

3.10 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 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. 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 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 take 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. 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, so it was appropriate to use a

conservative estimate for this assumption. It concluded that an at-risk period for HIV acquisition of 10 years was appropriate.

Transitioning from cabotegravir to TDF/FTC

3.11 The company's economic model allowed people in the cabotegravir arm, who were also in the subpopulation of those not taking 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 having alternative non-long-acting forms of PrEP in the months after stopping cabotegravir. In the company's cost-effectiveness analysis, a proportion of this group of people transitioned to TDF/FTC. The company considers the exact proportion to be confidential, so it could not be reported here. 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 could not 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. A clinical expert explained that most people who would prefer cabotegravir injections over oral PrEP would still take oral PrEP if it was the only option. For this reason, the expert commented that it would be appropriate to allow a proportion of people in the cabotegravir arm to transition to TDF/FTC after stopping cabotegravir. The committee noted that the company's proposed positioning included people who do not take oral PrEP exactly as prescribed for various psychosocial and lifestyle issues, and these issues may still be relevant if cabotegravir was stopped. The committee noted that 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. The committee concluded that it was appropriate to allow some people to transition from cabotegravir to

TDF/FTC, but there was uncertainty around the exact proportion that should transition and it was unlikely to be as high as the company assumption.

Improved persistence with cabotegravir

3.12 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 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 persistence for cabotegravir assumed in the company model. The company also noted that 2 US-based real-world studies showed persistence to cabotegravir to be 93% and 94%. The company's clinical experts had also commented that a 20% improvement in persistence with cabotegravir compared with oral PrEP was a reasonable assumption. The EAG preferred to assume that persistence with cabotegravir was equal to oral PrEP. It commented that there was no evidence directly comparing cabotegravir persistence with oral PrEP. The EAG also noted limitations with the company's 2 US-based real-world studies, including the definition of discontinuation and the company's interpretation of persistence. The clinical experts commented that they expected persistence with cabotegravir to improve compared with oral PrEP. They explained that clinicians 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. It was also 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 oral PrEP were equal at 12 months. The committee concluded that there would likely be an improvement in persistence with cabotegravir but there was uncertainty around the percentage improvement. It also noted that if the company's analyses were to include the whole population eligible for cabotegravir, including those who currently take oral PrEP exactly as prescribed (see section 3.3), there would be a much smaller improvement in persistence with cabotegravir.

Adherence to TDF/FTC

3.13 Adherence refers to the extent to which the person takes a medicine as agreed with their prescriber. In the company model it was assumed that adherence to TDF/FTC was lower for cis women compared with 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 have lower levels of engagement 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 considered 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 compared with MSM and trans women.

Starting age of people in the model

3.14 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 UK Health Security Agency (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 about the 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

3.15 In the company 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 only take 20 minutes, 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

3.16 In the company 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 clinicians 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 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

only be applied to the cabotegravir acquisition costs and not TDF/FTC. The committee concluded that it was not appropriate to apply a 5% increase to cabotegravir acquisition and administration costs.

Utility values

Disutility of living with HIV

3.17 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 on the basis of 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. (2014) 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 in populations without a high level of HIV awareness. 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 EAG's preferred disutility values for living with HIV were plausible. It noted that there were limitations with both the company's and EAG's evidence sources and that the most appropriate disutility value could lie between the company's and 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

3.18 PrEP is currently administered in level 3 sexual health services (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 was aware that commercial arrangements may affect implementation of cabotegravir in practice. It acknowledged the importance of ensuring those who need PrEP have adequate access to any new PrEP options.

Severity

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

Cost-effectiveness estimates

The committee's preferences and cost-effectiveness estimates

3.20 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 EAG's base cases differed on several assumptions. The company's base case 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 incremental cost-effectiveness ratio (ICER) was substantially above £30,000 per quality-adjusted life year (QALY) gained when compared with TDF/FTC. This reflected higher total costs of cabotegravir with relatively small modelled QALY gains. The EAG also calculated a cost-effectiveness estimate using a scenario analysis with no PrEP as a comparator. This estimated that cabotegravir was dominant

when compared with no PrEP. The committee preferred the model to include:

- both TDF/FTC and no PrEP as comparators
- a baseline HIV acquisition value of 3.9 per 100 person-years
- a HIV risk period of 10 years
- adherence to TDF/FTC to be lower for cis women compared with MSM and trans women
- 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 committee noted uncertainty around the exact proportion of people who should transition to TDF/FTC after stopping cabotegravir, and the percentage improved persistence that should be applied to those that have cabotegravir. The committee also noted a high level of uncertainty around whether the company's clinical trial data could be applied to a population who cannot take oral PrEP because of medical contraindications or difficulties swallowing tablets. It also commented that people who do not take oral PrEP exactly as prescribed cannot be identified in clinical practice by defined characteristics. It could not make a recommendation for subpopulations that could not be clearly defined and separated from one another. So, the committee concluded that to determine the cost-effectiveness of cabotegravir, it would be necessary for the company to present a cost-utility analysis using the whole population eligible for cabotegravir, including those who take oral PrEP exactly as prescribed. The committee noted that this cost-utility analysis should use the committee's preferred assumptions.

Other factors

Equality

3.21 The committee considered 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. 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, 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. The committee also noted that its recommendation does not restrict access to treatment for some people over others. The committee agreed that these were not potential equality issues that could be addressed in the recommendations.

Uncaptured benefits

3.22 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

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

4 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.

Giacomo De Guisa
Technical lead

Alexandra Filby
Technical adviser

Celia Mayers
Project manager

Ian Watson
Associate director

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