National Institute for Health and Care Excellence

Health Technology Evaluation

Cabotegravir injections for preventing HIV-1 in adults and young people [ID6255]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	BHIVA	None	No action required.
	CHIVA	Appropriate evaluation and evaluation route	Comment noted. No action required.
	Gilead	Gilead are fully aligned with the government's ambition of getting to zero new HIV transmissions by 2030 however Gilead believe that NICE is not an appropriate route for review for this technology for the following reasons: • Cabotegravir for PrEP is a public health and HIV prevention intervention and as such the evaluation is not how effective the medicine is in managing the patient living with a specific condition • NICE has limited experience in HIV-related technologies • NHSE have already produced a PrEP policy which includes both available generic and branded oral PrEP options therefore this technology could potentially be incorporated within this policy.	Comments noted. This topic has come through scoping at NICE and been agreed to be appraised as an STA. Using cabotegravir for preventing HIV is a significant license extension for the technology.

Section	Stakeholder	Comments [sic]	Action
		Gilead would welcome discussions with NHSE on the most appropriate evaluation route as part of a wider HIV elimination strategy	
	HIVPA	HIVPA suggest that this evaluation mirrors the US marketing authorisation and considers use those in those over 12, rather than 18, with the wording this for adults and adolescents 35kg and over. The pharmacokinetic data support this use and this will ensure this important group is not overlooked and access isn't compromised. We would support and encourage a technology appraisal in this situation as this is the first available injectable drug for HIV prevention.	Comments noted. NICE will appraise cabotegravir within its UK marketing authorisation.
	LGBT Foundation	It is appropriate for NICE to appraise Cabotegravir Injectable PrEP as a new HIV prevention tool, via the single technology appraisal pathway. From an equity standpoint, oral PrEP has been incredibly important but uptake limited among risk populations outside of gay and bi men. There are a range of potential barriers which could be addressed by injectable PrEP to increase uptake in key populations such as trans people, men who sleep with men (MSM) but who do not identify as gay or bisexual, sex workers, and homeless people. Among these groups, there are individuals for whom oral prep could pose a safety risk if found, for example by domestic abuse perpetrators or homophobic/biphobic family. There are also individuals who are unable to remain consistent with an oral treatment regimen for a range of reasons but would benefit from injectable PrEP. In addition to reducing HIV incidence in these individuals, the risk of treatment resistant HIV infection is also reduced	Comments noted. No action required.

Section	Stakeholder	Comments [sic]	Action
		if long-acting injectables are used due to the decreased possibility for missed doses. Cabotegravir injectable PrEP also provides an alternative to daily dosing oral PrEP for those who are unable to event-based dose due to their risk type (e.g. those with risk from vaginal sex for whom event-based dosing is less effective) – further reducing inequities in access and choice.	
	NHIVNA	Agreed with the process highlighted in the relevant documents	Comment noted. No action required.
	NHSE	It is very appropriate for NICE to consider the first ever non-tablet PrEP option, particularly as injectable cabotegravir (IM-CAB) has been demonstrated to be superior to oral PrEP in randomised trials. What is challenging is that, where investigated, IM-CAB generally has not been shown to be cost-effective and determining which population(s) will benefit most in a low HIV prevalence country like the UK will be challenging. Clear guidance around where this option sits relative to existing options (tenofovir-alafenamide/emtricitabine NHSE policy, tenofovir-disoproxil/emtricitabine generic) will be essential.	Comments noted. NICE will consider the clinical and cost-effectiveness of the technology within England. NICE does not intend to provide recommendations on existing options such as oral PrEP. There is already an existing NHSE policy for oral PrEP https://www.england.nhs.uk/wp-content/uploads/2020/10/2112-PrEP-policy-statement-version-2.pdf

Section	Stakeholder	Comments [sic]	Action
	Terrence Higgins Trust	It is absolutely appropriate and necessary for long-acting injectable cabotegravir (CAB-LA) to be evaluated. Results from HPTN033 and HPTN034 found CAB-LA to be superior (primarily by way of improved adherence and therefore greater reduction of HIV infection within study cohorts) to oral TDF/FTC in men and trans women who have sex with men (033) and women and people assigned female at birth. (044). Particularly from an equity and equalities perspective, in regards to HIV PrEP options which are both effective and have high acceptability in women. Previous trials of oral PrEP in women (while limited) showed daily oral PrEP (both TDF and TDF/FTC) to be far less effective than in oral PrEP trials in men who have sex with men (MSM). https://bmjopen.bmj.com/content/12/5/e048478 Effectiveness in MSM Six studies enrolled MSM.3 5 6 20 21 25 A meta-analysis of all studies resulted in an RR of 0.25 (95% CI 0.1 to 0.61), indicating a 75% reduction in the rate of HIV acquisition (figure 3). The estimated absolute RD was −0.03 (95% CI −0.01 to −0.05), indicating PrEP users had a 3% lower rate of HIV acquisition per person-year of follow-up. When stratified by adherence (≥80% vs <80%), heterogeneity was eliminated (I2 reduced from 52% to 0%). PrEP was most effective in studies with high adherence (≥80%), as expected, where the rate of HIV acquisition was reduced by 86% (RR 0.14, 95% CI 0.06 to 0.35; RD −0.06, 95% CI −0.04 to −0.09; I2=0%, n=3 studies).5 6 21 Of the three studies with high adherence, one study was small and reported non-significant findings due to few events (Mutua et al21). Of the remaining two studies, one study investigated daily	Comments noted. No action required.

Section	Stakeholder	Comments [sic]	Action
		PrEP use (McCormack et al, PROUD trial)6 and the other investigated on-demand PrEP (Molina et al, IPERGAY trial).5 Both studies reported identical efficacy (PROUD: RR 0.14, 95% CI 0.04 to 0.47; IPERGAY: RR 0.14, 95% CI 0.03 to 0.6). When adherence was under 80%, acquisition rate was reduced by 45% (RR 0.55, 95% CI 0.37 to 0.81; RD −0.01, 95% CI −0.00 to −0.02; I2=0%, n=3 studies).3 20 23 25 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5175411/ *“Five major randomized trials of oral PrEP have included women.3–7 Of these five, three reported evidence of effectiveness in the women’s subgroups (Figure 1). Partners PrEP3 showed a significant reduction in risk of HIV acquisition among women (both TDF and TDF/FTC), while both TDF2-Botswana4 and Bangkok-TDF5 showed non-significant trends toward reduced risk. The other two major trials, VOICE6 and FEM-PrEP7 were conducted only in women, and showed no reduction in risk.” Various factors may explain the conflicting results observed in women, including drug adherence, differences in the study populations such as participant type (discordant couples versus uninfected individuals), demographic and behavioral characteristics, prevalent HIV subtypes, transmission mode (mucosal versus parenteral), and underlying host factors such as genital-tract inflammation and/or the presence of co-pathogens.* Part of the reason for low or no effectiveness in these trials of oral PrEP in women is physiological. The IPERGAY trial in MSM showed that, for anal sex, the lead-in time to protective levels of drug, after taking a 2 pill loading	

Section	Stakeholder	Comments [sic]	Action
		dose was 2 hours and required only 2 subsequent doses of a single pill (24 and 48 hours after initial double dose) to safely stop PrEP (for an individual sexual event, or 24 and 48 hours after last risk of exposure for a prolonged period). Whereas vaginal sex requires a much longer lead-in time. Current BASHH BHIVA PrEP guidelines recommends a single pill for 7 days before sex. Daily dosing (1 pill per day) during period of risk/possible exposure, and 7 days of daily dosing (1 pill per day) after last risk, to safely stop PrEP. This guidance is based on pharmacokinetic data and could possibly change in the updated guidelines, due late 2023. https://www.bhiva.org/file/5b729cd592060/2018-PrEP-Guidelines.pdf **4.6 Evidence for the timelines for starting and stopping PrEP** Evidence for the timelines for starting and stopping PrEP: summary • The time to achieve a protective concentration is determined by the drugs used, the dose, the frequency of dosing and the target tissue. • Available data suggest that time to clinical protection for TDF and FTC (and active metabolites) is shortest in the lower gastrointestinal tract, followed by peripheral blood mononuclear cells (FGT) and then in the female genital tract (FGT). • The active metabolite of TDF concentrates to much higher levels in the lower gastrointestinal mucosa relative to PBMCs whereas FTC concentrates in the FGT.	

Section	Stakeholder	Comments [sic]	Action
		• The time to clinical protection for anal sex has been evaluated in a single RCT (IPERGAY), starting with a double dose of TDF-FTC 2–24 hours before sex. This is supported by pharmacokinetic data in animal studies. • The time to clinical protection for vaginal sex has been extrapolated from pharmacokinetic studies of TDF-FTC and there is consensus for a lead-in time for protection of 7 days. • Data from IPERGAY demonstrate that, when PrEP is taken to prevent HIV acquisition from anal sex, dosing can be stopped when an oral dose has been taken 24 hours and 48 hours after the last episode of potential exposure. This is supported by animal and pharmacokinetic studies when the person is receptive, but there are fewer data for foreskin and urethra. • There is consensus that, when taken to prevent HIV acquisition from vaginal sex, TD-FTC can be stopped when a daily oral dose has been taken for 7 days after the last episode of potential exposure. There are several well-conducted pharmacokinetic studies which have used diverse methodology to address the question of time to clinical protection. There is considerable heterogeneity across study results, but a consensus has emerged with respect to: (i) The concentration of the active metabolites of TDF and FTC in colonic and cervico-vaginal tissue relative to PBMCs; (ii) The shorter time it takes to achieve the peak concentration of FTC-TP compared to TFV-DP; and	

Section	Stakeholder	Comments [sic]	Action
		(iii) The longer half-life of TFV-DP in all tissues. There is also consensus that concentrations of active metabolites in the genital and colonic tissues are probably the most important in averting infection. Part of the reason for low/no effectiveness is behavioural and social. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5175411/ *"Various factors may explain the conflicting results observed in women, including drug adherence, differences in the study populations such as participant type (discordant couples versus uninfected individuals), demographic and behavioral characteristics."* It would be prudent to acknowledge that the biological, behavioural, and social barriers to PrEP effectiveness for those who are currently under-represented and/or underserved in HIV prevention services can only be mitigated by increasing the choices available to those individuals and communities. Increasing equitable access in settings and within services already accessed by those people or where acceptability has been established is as important as commissioning novel PrEP technologies. CAB-LA is the first and only PrEP modality that has proved highly effective in women, in all PrEP studies to date. https://www.aidsmap.com/about-hiv/prep-and-women	

Section	Stakeholder	Comments [sic]	Action
		"HPTN 084 was the phase III study set up to measure the effectiveness of injections every two months of a long-acting formulation of an antiretroviral, cabotegravir, which is already one of the two drugs used in injectable HIV treatment. *Results in the companion study, HPTN 083 in gay and bisexual men and trans women, were already very promising – the cabotegravir injections were 70% more effective than TDF/FTC pills.* *But HPTN 084's results were not so much promising as groundbreaking. The effectiveness of the injections was over 90% – meaning that for every one infection stopped by the oral TDF/FTC PrEP in the other study arm, the injections stopped at least nine.* *HPTN 084 demonstrated not only by far the best effectiveness seen in any study of PrEP in women, it is the best ever reported for any randomised, placebo-controlled study of PrEP.* *Since then, the promise of injectable PrEP for women has only been magnified by recent findings. During a further year of open-label follow-up, no more women acquired HIV while on cabotegravir. Indeed, one woman originally classed as a 'breakthrough' infection was found to have acquired HIV before joining the study, raising the effectiveness from 88% to 92%.* *In HPTN 083 (the study with gay and bisexual men and trans women), there were a handful of puzzling HIV infections in participants who became infected despite having efficacious blood levels of PrEP. There have been none so far among the women taking part in HPTN 084, and only one infection in a woman with cabotegravir levels even slightly above averagely protective levels.*	

Section	Stakeholder	Comments [sic]	Action
		This suggests that injectable cabotegravir might not just be more effective in women, it might be more intrinsically efficacious. A 2023 study found that once the two-monthly injections began, drug levels in women were 32% higher than in men. In only 2% of women who had injections up to a month late did drug concentrations in blood fall to levels that might even possibly be ineffective. This opens the door to quarterly PrEP injections for women – which would synchronise with existing regimens for injectable contraceptives. *It is important to emphasise that this does not just attest to the efficaciousness of injectable PrEP. Retention in the study was excellent, with only 6% of women (in either arm) discontinuing permanently in the first year. In women on the cabotegravir arm, 11% missed one or more of their injections or had it more than four weeks late, but most only missed one. This means that the injections did not just work medically; they fitted in with the lifestyles and priorities of the women who took part in this study, who were happy to come to the clinic to receive them.* https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00538-4/fulltext *"In summary, the HPTN 084 trial provides robust evidence that cabotegravir has an acceptable safety profile, is well tolerated, and is superior to TDF-FTC in preventing HIV infection in women in sub-Saharan Africa. Given the urgent need for an expanded range of effective options for HIV prevention in women, these data support the inclusion of injectable cabotegravir as an additional choice, particularly for women in high-incidence settings where the need is greatest."* **UKHSA Official Statistics**	

Section	Stakeholder	Comments [sic]	Action
		HIV testing, PrEP, new HIV diagnoses, and care outcomes for people accessing HIV services: 2022 report (data to end of December 2021): https://www.gov.uk/government/statistics/hiv-annual-data-tables/hiv-testing-prep-new-hiv-diagnoses-and-care-outcomes-for-people-accessing-hiv-services-2022-report *"Among the 2,023 new HIV diagnoses first made in England men exposed through sex between men accounted for 36% (721), women exposed by heterosexual contact for 21% (429), men exposed by heterosexual contact for 18% (369), injecting drug use for 2% (45), those exposed by vertical transmission, for 0.7% (15), and those exposed by blood products for a further 0.4% (10).* *Between 2020 and 2021, the number of new HIV diagnoses first made in England in women exposed by heterosexual contact rose by 9% (392 to 429), and increased slightly from 367 to 369 among men exposed by heterosexual contact. This is despite only modest increases in HIV testing in these groups, especially men exposed by heterosexual contact, suggesting transmission has not declined in these populations."* https://www.aidsmap.com/about-hiv/prep-and-women in the UK, although 2.5% of people in the UK are of Black African ethnicity and 4% of any Black ethnicity, 42% of heterosexual HIV infections are among Black Africans. In 2020, for the first time in a decade, diagnoses in heterosexuals exceeded those in gay men and 28% of all new diagnoses in the UK are now among cisgender heterosexual women.	

Section	Stakeholder	Comments [sic]	Action
		PrEP has been routinely available via sexual health services, initially in Scotland (April 2017), Wales (July 2017), and England (October 2020). In Northern Ireland, PrEP is not routinely available but is provided by an extended pilot. However, the 2022 'Not PrEPared' report from UK community organisations National AIDS Trust (NAT), Terrence Higgins Trust (THT), PrEPster, Sophia Forum, and One Voice Network found huge unmet need for PrEP. https://www.nat.org.uk/sites/default/files/publications/Not%20PrEPared.pdf The report provides the results of three surveys; • PrEP service users and those seeking to use PrEP (community) • Clinicians involved in providing PrEP • Sexual health service commissioners and providers across the UK The research identified that communities beyond gay and bisexual men are still not aware of PrEP. No local authority reported more than 5 women using their PrEP services. Similarly, only 12 of the 1,120 community survey respondents (1%) were women. The PrEP IMPACT Trial which ran in England from October 2017 to July 2020 enrolled 24,255 participants. The majority were gay and bisexual men (GBM). IMPACT reported 87% fewer HIV infections in GBM than a comparable group of sexual health clinic attendees who did not take PrEP.	

Section	Stakeholder	Comments [sic]	Action
		Only 1,038 PrEP IMPACT Trial participants (4.3%) were not within the GBM group. https://www.aidsmap.com/news/apr-2021/englands-big-prep-implementation-trial-releases-its-enrolment-data-young-people-under Of the 1,038; • 359 (34.6%) were transgender women • 333 (32.1%) were cisgender women. • 152 (14.6%) were transgender men • 150 (14.5%) were cisgender men. • 35 (3.4%) were non-binary The World Health Organisation (WHO) guidance on long-acting injectable PrEP recommends offering CAB-LA as an additional PrEP choice in order to increase potential for uptake and for effective PrEP use. Guidelines on long-acting injectable cabotegravir for HIV prevention (who.int) We would expect the evaluation route for CAB-LA to be 'single technology appraisal'.	
	UK-CAB (joint response)	HIV remains a life-long, life-changing long-term condition, and whilst people who acquire HIV today have access to effective HIV treatment, there is still potential impact of their long-term health, including their mental wellbeing due to internalised, societal and structural HIV-related stigma. It is appropriate for NICE to appraise and review new and novel clinical HIV prevention interventions, and in the case of Cabotegravir Injectable via the single technology appraisal route. Oral-based PrEP has been a game-changer in England's HIV response, but the gains have largely been focused on gay and bisexual men.	Comments noted. No action required.

Section	Stakeholder	Comments [sic]	Action
		Cabotegravir injectable as PrEP will provide opportunities to prevent HIV in people for whom current oral-based PrEP is not suitable, whilst likely having the potential to raise more awareness about HIV prevention interventions amongst the general public. Cabotegravir as injectable PrEP has been proven to be more effective than oral-based PrEP (see trials HPTN033 and HPTN034). Cabotegravir Injectable provides an equitable method of providing PrEP to people at high-risk of HIV regardless of the type of sex they have (e.g. vaginal and anal) or their gender. Not all oral-based PrEP dosing methods are clinically effective in all people, or for all types of sex. In particular women are more likely to be affected by poor adherence to oral-based PrEP, increasing their risk of acquiring HIV.	
	ViiV Healthcare	Yes, an STA is the appropriate route. The topic is highly relevant and timely as the prevention of HIV infections remains a key priority for the NHS illustrated by the commitment to zero new transmissions of HIV by 2030 in the HIV Action Plan for England 2022 to 2025.[1]	Comments noted. No action required.
Wording	BHIVA	None	No action required.
	CHIVA	Suggest adding “sexually active adult and young people as per label	Comment noted. NICE will appraise cabotegravir within its UK marketing authorisation.

Section	Stakeholder	Comments [sic]	Action
	Gilead	Gilead notes that this technology is being assessed within its marketing authorisation	Comment noted. No action required.
	HIVPA	As above, we suggest that the scope includes adults and adolescents aged over 12 and over 35kg.	Comment noted. NICE will appraise cabotegravir within its UK marketing authorisation.
	LGBT Foundation	It is key to consider the holistic benefits of PrEP use including mental and emotional health for individuals, not solely cost effectiveness and clinical effectiveness.	Comment noted. The committee will consider all relevant health-related quality of life outcomes when appraising the technology.
	NHIVNA	No comment – the wording appears in line with international standards	Comment noted. No action required.
	NHSE	The commissioning model for HIV PREP is complex, with PrEP service provision commissioned by Local Authorities, and PrEP drugs funded by NHS England Specialised Commissioning. The remit lacks detail. A concern expressed during consultation for IM-CAB/RPV as treatment for HIV (NICE TA757) that was not addressed was related to the non-drug costs of providing injectable treatment. The same applies here – particularly as IM-CAB could potentially be delivered in specialist sexual health services (SHS) which have seen a marked reduction in funding as part of cuts to the Public Health grant. The surge in demand on	Comments noted. The appraisal committee will consider implementation costs throughout the appraisal. NHSE should provide NICE with relevant estimates for implementation costs during the appraisal.

Section	Stakeholder	Comments [sic]	Action
		SHS during the mpox outbreak highlighted that Local Authority commissioners can/will not provide extra funding for new activity. SHS will not be able to absorb the potential extra work of delivering injectables, provide the additional testing (IM-CAB requires regular viral load monitoring to check for new HIV acquisition, unlike oral PrEP for which serology is sufficient, this has additional costs) without an associated tariff that covers the additional activity. An additional consideration is, if the drug is accessed via primary care, and a commercial arrangement is required, sexual health clinics *may* not be able to access discounted prices. As such, any appraisal must include the additional costs of arranging, delivering and monitoring IM-CAB PrEP. It is critical to consider any absolute, as well as relative, benefit of IM-CAB over current options. Presumably that will be the case but in the absence of further detail in the remit, the HIV Clinical Reference Group (CRG) wishes to flag this concern.	
	Terrence Higgins Trust	WHO guidelines on PrEP and 'substantial risk' states "When PrEP use is risk-informed (taken during periods of risk of HIV acquisition), PrEP can be cost-effective. Cost-effectiveness will vary across countries, populations, and PrEP products. However, cost–effectiveness should not be the only consideration when implementing PrEP programmes, since remaining HIV-negative and having control over HIV risk has intangible value to people and communities." Guidelines on long-acting injectable cabotegravir for HIV prevention (who.int)	Comments noted. Costs outside of the NHS and Personal Social Services perspective fall outside of the reference case set out in NICE health technology evaluations: the manual. The manual notes that some technologies may have

Section	Stakeholder	Comments [sic]	Action
			substantial benefits to other government bodies. Evaluations that consider benefits to the government outside of the NHS and PSS will be agreed with the Department of Health and Social Care and other relevant government bodies as appropriate. They will be detailed in the remit from the Department of Health and Social Care and the final scope. The NICE board also discussed adopting wider societal perspectives during its December 2022 public board meeting. The board supported the recommendation to retain the current approach to economic analyses. The minutes can be found on the NICE website.

Section	Stakeholder	Comments [sic]	Action
	UK-CAB (joint response)	Clinical effectiveness should consider wider health and societal benefits, "remaining HIV-negative and having control over HIV risk has intangible value to people and communities" (Guidelines on long-acting injectable Cabotegravir for HIV prevention, WHO, July 2022). The removal of fear and anxiety from sex, by providing protection for people at high-risk from a life-long long-term condition such as HIV should not be underestimated.	Comments noted. The committee will take the removal of fear and anxiety from sex into account during the appraisal.
	ViiV Healthcare	ViiV Healthcare proposes amending the draft remit wording to align with the target population for this appraisal: "To appraise the clinical and cost effectiveness of cabotegravir as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals for whom oral PrEP is not appropriate."	Comments noted. The remit wording states that the technology will be appraised within its marketing authorisation. No action required.
Timing issues	BHIVA	None	No action required.
	CHIVA	This could be answered based on incidence rate of HIV in UK (# new preventable infections) alongside UK national strategy for coverage and the gap between proportion of individuals with indication for PrEP and proportion of individuals aware and willing to or using PrEP (Sullivan P, J Int AIDS Soc, 2020 Mar;23(3):e25461. doi:10.1002/jia2.25461)	Comment noted. No action required.
	Gilead	The HIV Action Plan (Towards Zero 2022 – 2025) states that the "provision of a wider choice of PrEP methods, including injectable versions may improve uptake, acceptability, and adherence. OHID will work with NHSEI and partners to monitor the potential use of new methods such as injectable PrEP as the evidence to support their effectiveness becomes available".	Comments noted. NICE aims to appraise cabotegravir for preventing HIV-1 in adults and young people to be as timely as possible in relation to

Section	Stakeholder	Comments [sic]	Action
		Given the government ambition of achieving zero HIV transmissions by 2030, if they continue with current practices the NHS will not meet this ambition so alternative therapies that can help reach this community will undoubtedly help with the government ambition.	the technology receiving its UK marketing authorisation.
	HIVPA	There is a need for access to this in order to prevent HIV transmission in a number of cases, this is demonstrated by access to cabotegravir for pre-exposure prophylaxis via a compassionate use scheme.	Comment noted. No action required.
	LGBT Foundation	HIV reduction is a key political and public health aim as stated in goals/documents such as the 'zero transmissions by 2030' aim, and the government's HIV action plan. Widened choice in HIV prevention tools is important to achieving this.	Comments noted. No action required.
	NHIVNA	Cabotegravir should be made available asap as it can address the needs of people who can't take oral PrEP	Comments noted. NICE aims to appraise cabotegravir for preventing HIV-1 in adults and young people to be as timely as possible in relation to the technology receiving its UK marketing authorisation.
	NHSE	There are currently two treatment options available for HIV PrEP. There is no perceived urgency for the evaluation of cabotegravir.	Comment noted. NICE aims to appraise cabotegravir for preventing HIV-1 in

Section	Stakeholder	Comments [sic]	Action
			adults and young people to be as timely as possible in relation to the technology receiving its UK marketing authorisation.
	Terrence Higgins Trust	In January 2019, the UK government committed to an ambition to end new HIV transmissions, AIDS diagnoses and HIV-related deaths within England by 2030. The HIV Action Plan, published in December 2021, set out how government aims to achieve an 80% reduction in new HIV infections in England by 2025. **Towards Zero - An action plan towards ending HIV transmission, AIDS and HIV-related deaths in England - 2022 to 2025** https://www.gov.uk/government/publications/towards-zero-the-hiv-action-plan-for-england-2022-to-2025/towards-zero-an-action-plan-towards-ending-hiv-transmission-aids-and-hiv-related-deaths-in-england-2022-to-2025 *"The government is committed to achieving zero new HIV infections, AIDS and HIV-related deaths in England by 2030* *This vital, highly stretching and world-leading ambition will require a doubling down on existing efforts and the adoption of new strategies to reach everyone we need to. We will need to maintain the excellent progress made with key groups – gay and bisexual men, younger adults, those in London – and significantly improve diagnoses for other groups. More progress is needed on heterosexuals, and black Africans remain the ethnic group with the highest rate of HIV, making them a priority for HIV prevention and testing."*	Comments noted. No action required.

Section	Stakeholder	Comments [sic]	Action
		WHO has similar ambitions: *"Achieving the Global AIDS target for 2025 of ensuring that 95% of people at risk of HIV acquisition have access to HIV prevention options requires a focus on expanding effective HIV prevention choices"*	
	UK-CAB (joint response)	Access and availability of novel HIV prevention interventions are important if England is to achieve its ambitious goals to reduce new HIV transmissions by 80% between 2019 and 2025, and the end them by 2030. Cabotegravir injections will support existing HIV prevention and testing efforts needed to meet these targets. Current pill-based HIV PrEP is not accessible or acceptable for all people during periods of time they might be at risk of HIV.	Comments noted. No action required.
	ViiV Healthcare	This appraisal should be considered with urgency. While oral PrEP is currently available in the NHS, some individuals may not be currently served by the existing oral PrEP options. Cabotegravir offers a much-needed new prophylaxis modality for people at risk of acquiring HIV-1. This includes both a new dosing frequency as a long-acting technology and a new administration as an injectable therefore cabotegravir may solve for unmet needs not achievable by current oral PrEP options. In addition, the timely appraisal of cabotegravir, for HIV prevention, is critical as this evaluation may offer further resources to support ongoing NHS initiatives to achieve the government's net zero HIV transmission goal, which was referenced above, and hence help to end the HIV epidemic	Comments noted. NICE aims to appraise cabotegravir for preventing HIV-1 in adults and young people to be as timely as possible in relation to the technology receiving its UK marketing authorisation.

Section	Stakeholder	Comments [sic]	Action
		This goal is aligned to the World Health Organization recommendation that cabotegravir should be delivered as an additional HIV prevention choice, as part of combination HIV prevention approaches, to support countries in achieving national targets of reducing new HIV infections.[2]	
Additional comments on the draft remit	BHIVA	None	No action required.
	CHIVA	- In addition to clinical and cost-effectiveness, impact on quality of life including stigma would be an important factor to consider, in addition to being included in the outcome measures section - Lifestyle of young people and challenges of adherence to any long-term medication in young people should be highlighted so this can be considered as an option when appropriate	Comments noted. The committee will consider all relevant health-related quality of life outcomes when appraising this technology.
	Gilead	None	No action required.
	HIVPA	None	No action required.
	LGBT Foundation	None	No action required.
	NHIVNA	None	No action required.
	NHSE	The draft scope (page 1) is not entirely accurate, breast milk transmission can occur when viral load is undetectable for example. On page 1 ‘at particular times’ would read better as ‘before and after sexual exposure’.	Comment noted. Wording has been updated to ‘HIV is transmitted through the body fluids of a person, usually with a detectable level of the virus’. Wording also

Section	Stakeholder	Comments [sic]	Action
			updated from 'at particular times' to 'before sexual exposure'. Tablets taken after exposure would refer to PEP (post-exposure prophylaxis).
	Terrence Higgins Trust	No	No action required.
	UK-CAB (joint response)	None	No action required.
	ViiV Healthcare	NA	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BHIVA	Given the relative costs and high efficacy of oral tenofovir/emtricitabine (TDF/FTC) it is likely that cabotegravir injections would be a second line option in people where TDF/FTC is likely to be less effective or where there are safety concerns with both TDF/FTC and tenofovir alafenamide/emtricitabine (TAF/FTC).	Comment noted. No action required.
	CHIVA	- Refer to PeopleFirst Charter https://peoplefirstcharter.org/ - suggest changing AIDS in first paragraph to: complications of advanced HIV, person with an AIDS-defining illness	Comment noted. Wording in the first paragraph has been

Section	Consultee/ Commentator	Comments [sic]	Action
		- Page 1 paragraph 2 – suggest changing sexually transmitted diseases to sexually transmitted infections. - Page 1 paragraph 3 please refer to latest UKHSA 2021 data https://www.gov.uk/government/statistics/hiv-annual-data-tables	updated to include 'complications of advanced HIV. The term AIDS has been kept in to align with the terminology used by NHS Wording updated to sexually transmitted infections The number of people living with HIV in the UK has been updated include statistics from the most recent accessible sources.
	Gilead	Gilead have no comments apart from the suggestion that using Tenofovir disoproxil (TDx) alone is suitable for PrEP which we note is not a licensed indication with the UK, or within Europe (EMA) or the US (FDA)	Comment noted. Off-label and unlicensed treatments are not automatically excluded as comparators. The company can make a case for which comparators are appropriate in their submission. The committee will consider which comparators are appropriate.

Section	Consultee/ Commentator	Comments [sic]	Action
	HIVPA	None	No action required.
	LGBT Foundation	Ensure HIV data remains up to date with most recent figures available	Comment noted. The number of people living with HIV in the UK has been updated include statistics from the most recent accessible sources.
	NHIVNA	Agreed	Comment noted. No action required.
	NHSE	There is a second line treatment option available for individuals who are not able to tolerate TDF-FTC, and who meet the eligibility criteria as outlined in the NHS England Reimbursement of PrEP policy	Comments noted. Wording in background has been updated to include this.
	Terrence Higgins Trust	**Background** Human Immunodeficiency Virus (HIV) is a virus that attacks the immune system by destroying CD4 positive T cells, a type of white blood cell that is vital for fighting infections. The destruction of these cells leaves people living with HIV unable to fight off infections and some other diseases and can result in acquired immune deficiency syndrome (AIDS). HIV is transmitted through the body fluids of a person with a detectable level of the virus (including semen, vaginal and anal fluids, blood and breast milk). The most common way of getting HIV for people treated in the NHS is sexual intercourse without a condom. The risk of transmission per exposure is low; estimates are on the order of 0.1% per contact for heterosexual transmission, but this varies considerably and increases with concurrent ulcerative sexually	Comments noted. The aim of the background section is to provide a very brief summary of the disease area. Further details can be included in all submissions for this appraisal. The addition of 'and after' has not been incorporated into the

Section	Consultee/ Commentator	Comments [sic]	Action
		transmitted diseases, high HIV viral load in the host, and lack of antiretroviral therapy.[1] There are two main types of HIV. Most cases within the UK are from the HIV-1 type and it is considered more transmissible than HIV-2. An estimated 103,800 people were living with HIV in the UK in 2018, of which 93% were diagnosed (95,500 diagnosed cases). Of these patients, 97% were receiving treatment (estimated 92,600) and 97% of these patients were virally suppressed (estimated 90,000).[2] - Should these figures be updated with 2022 data and the latest 90-90-90 stats. HIV prevention includes a mix of behavioural, biomedical and structural interventions. Pre-exposure prophylaxis is the use of treatments to prevent infection in people who have not yet been exposed. For HIV, this is known as PrEP. Taking PrEP before and after HIV exposure can prevent HIV from getting into the body and replicating.[3] NICE guideline 221, on reducing sexually transmitted infections recommends that PrEP is offered to people at higher risk of HIV using the criteria in the British HIV Association / British Association for Sexual Health and HIV (BHIVA/BASHH) guidelines. - The guidelines steering group/chairs are meeting 07/08/23 and the updated guidelines are due to go out for public consultation soon after. Normally treatment involves taking tablets every day (daily PrEP) but in some cases, it may mean taking tablets at particular times (event-based or on-demand PrEP).[4] BASHH recommends the use of tenofovir disoproxil (TD) and emtricitabine (FTC). TD can be used alone or in combination where it is known as TD-FTC or TDF-FTC. PrEP is used as part of combination HIV prevention.[5] Where HIV infection occurs, NICE has also appraised and recommends the use of cabotegravir with rilpivirine as an option for treating HIV-1 infection in adults (TA757).	scope, as this would refer to post-exposure prophylaxis (PEP). Wording has been updated to 'BASHH also recommends that TD alone can also be offered to heterosexual men and women where FTC is contraindicated, but not to men who have sex with'.

Section	Consultee/ Commentator	Comments [sic]	Action
		Do we need to give context here as TD alone is not indicated for use as HIV PrEP in all groups. https://www.bhiva.org/file/5b729cd592060/2018-PrEP-Guidelines.pdf **3 Summary of recommendations** **4.1 Evidence for safety and efficacy in men who have sex with men (MSM): recommendations** 1. We recommend that PrEP with on-demand or daily oral TD-FTC should be offered to HIV-negative MSM who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 6 months and ongoing condomless anal sex. (1A) 2. We recommend that PrEP with on-demand or daily oral TD-FTC should be offered to HIV-negative MSM having condomless anal sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A) 3. We suggest that tenofovir alone should not currently be offered as PrEP to MSM. This recommendation is based on lack of evidence, rather than evidence of lack of effect. (2C) **Good practice point**	

Section	Consultee/ Commentator	Comments [sic]	Action
		• Consider PrEP on a case by case basis in MSM with current factors other than condomless anal sex in previous 6 months that may put them at increased risk of HIV acquisition. See Section 5. **4.2 Evidence for safety and efficacy in heterosexual populations: recommendations** 4. We recommend that daily oral TD-FTC should be offered to HIV-negative heterosexual men and women having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A) 5. We suggest that PrEP with daily oral TD-FTC should be offered on a case-by-case basis to heterosexual men and women with current factors that may put them at increased risk of HIV acquisition. See Section 5.1. (2B) 6. We recommend that TDF alone can be offered to heterosexual men and women where FTC is contraindicated. (1A)	
	UK-CAB (joint response)	The background information is largely accurate and complete. Feedback: 'The most common way of getting HIV for people treated in the NHS is sexual intercourse without a condom' – This should also include 'without other proven HIV prevention interventions, including oral-based PrEP'.	Comments noted. Wording updated to 'The most common way of getting HIV for people treated in the NHS is sexual intercourse without a

Section	Consultee/ Commentator	Comments [sic]	Action
		HIV data: Currently the figures include 2018 data, surveillance information is available from UKHSA up to 2021, which more accurately reflects the current HIV epidemic in the UK – in particular taking into account the impact of the COVID-19 pandemic.	condom or other proven HIV prevention interventions'. The number of people living with HIV in the UK has been updated include statistics from the most recent accessible sources.
	ViiV Healthcare	ViiV Healthcare suggests the following amends or additions are made for improved accuracy and completeness: **<u>Background information - Paragraph 2: ViiV suggests replacing this sentence</u>**: "The risk of transmission per exposure is low; estimates are on the order of 0.1% per contact for heterosexual transmission, but this varies considerably and increases with concurrent ulcerative sexually transmitted diseases, high HIV viral load in the host, and lack of antiretroviral therapy." **With:** "There is almost zero risk of sexual transmission of HIV with viral loads of less than 1000 copies per mL [1], with no sexual transmissions in cases involving less than 600 copies per mL and exceedingly rare in cases of less than 1000 copies per mL [2]. In the context of higher viremia, the risk of HIV acquisition varies widely dependent on the route of transmission and risk is modified by certain factors such as condoms [3]. Systematic review evidence identifies sexual exposure risks range from low for oral sex to 138 infections per 10,000 exposures for receptive anal intercourse [3]."	Comments noted. The aim of the background and technology sections are to provide a very brief summary of the disease area. Further data and information can be provided at the submission stage of the appraisal. Wording has been updated to note that the NHS England commissioning policy on PrEP for the prevention of HIV recommends

Section	Consultee/ Commentator	Comments [sic]	Action
		Justification: it is important to differentiate the risk of transmission from a person who has an undetectable vs detectable viral load since this plays an important risk factor, if a person is undetectable the risk of transmission is 0 (zero) [3-5]. Furthermore, it would be inappropriate to focus the description of the transmission risk on the heterosexual population given that the scope of this appraisal is not limited to this population. **Background information – Paragraph 5, ViiV recommends replacing the sentence**: "BASHH recommends the use of tenofovir disoproxil (TD) and emtricitabine (FTC). TD can be used alone or in combination where it is known as TD-FTC or TDF-FTC. PrEP is used as part of combination HIV prevention." **With "**The licensed HIV pre-exposure prophylaxis (PrEP) regimen and standard of care is the use of antiretroviral drugs called tenofovir disoproxil (TD) and emtricitabine (FTC) used in combination known as TD-FTC. PrEP trials have also evaluated tenofovir disoproxil fumarate (TDF) and FTC used in combination known as TDF-FTC. Other salts of tenofovir disoproxil (including maleate, succinate and phosphate) can be used in generic formulations. A second line regimen, licensed for a limited population (men who have sex with men) is tenofovir alafenamide (TAF) and emtricitabine (FTC) used in the combination known as TAF-FTC. Not licensed but included in BHIVA/BASSH guidelines, tenofovir monotherapy regimens including TD or TDF alone, can be considered only for heterosexual men and women. In this response we will use tenofovir to represent all oral PrEP regimens. Furthermore, the specialised clinical commissioning policy for PrEP constitutes the current	alafenamide (TAF) in combination with FTC as a second line option where TD-FTC is contraindicated. The technology brand name has been updated to Apretude.

Section	Consultee/ Commentator	Comments [sic]	Action
		standard of care and only outlines the use of tenofovir in combination with emtricitabine (TDF/FTC and TAF/FTC)[6] *Justification*: the distinction between tenofovir monotherapy and in combination is important since the guidelines identify that tenofovir (TDF) alone should not be offered as PrEP to men who have sex with men (MSM), nor is it licensed for this use and any use would represent a small population of PrEP use in England and Wales. **The technology - Paragraph 1:** Replace "Vocabria" **with** "Apretude" in the first sentence. *Justification*: see rationale described below (The technology, paragraph 3). **The technology - Paragraph 2:** Replace "female adults who are living without HIV, as well as men who have sex with men and transgender women at high risk of sexually acquired HIV" **with** "people who are living without HIV at risk of sexually acquiring HIV, including populations such as gender diverse people and ethnic minorities." *Justification*: this is in line with the BHIVA Inclusivity statement: "We recognise the importance of these guidelines being inclusive and relevant to all, regardless of sexuality or gender identity or expression. For the sake of brevity in the main text of the guidelines, phrases such as 'men who have sex with men' refer to cis-gender or non-binary or gender-queer men who have sex with men and 'heterosexual men and women' refers to cis-gender or non-binary or gender-queer men and women who have heterosexual sex. Where sections are specifically relevant to trans people, we identify this using the terms trans people, trans men or trans women."[7]	

Section	Consultee/ Commentator	Comments [sic]	Action
		The technology - Paragraph 2: For completeness, it is relevant to add that the trials involving cabotegravir as prevention compared cabotegravir intramuscular injections as well as an oral placebo (not standard of care) against injectable placebo on top of standard care (TDF/FTC). **The technology - Paragraph 3**: Add the commercial name for cabotegravir injection for the treatment of HIV-1, in combination with rilpivirine injection: "Cabotegravir (Vocabria), is administered as an intramuscular injection in combination with rilpivirine (Rekambys) injection". *Justification:* [redacted] Vocabria is the brand name for cabotegravir long acting injectable licensed for use only in combination with rilpirivine (Rekambys) long acting injectable for the treatment of HIV-1. The Vocabria tablet has marketing authorisation as an optional oral lead-in for treatment of HIV-1. [redacted]	
Population	BHIVA	None	No action required.
	CHIVA	Defining young people would be important – e.g. weighing at least 35kg as per CAB PrEP FDA/EMA licensing	Comment noted. The population is intentionally kept broad

Section	Consultee/ Commentator	Comments [sic]	Action
		And in line with age of consent to take part in sexual activity / 16 years?	to avoid excluding potentially eligible people. NICE will however only appraise the technology within its marketing authorisation.
	Gilead	Gilead notes the population are people at risk of sexually acquired HIV. Whilst we note that this is consistent with the likely indication for cabotegravir for PrEP, as well as other oral PrEP regimens, this population is not the only one at risk of acquiring HIV. Consideration should be given to the role of novel injectables in preventing non-sexual acquisition of HIV, for example for people who inject drugs. This could support wider global and UK government ambitions of getting to zero HIV transmissions by 2030.	Comments noted. NICE will appraise cabotegravir within its marketing authorisation.
	HIVPA	None	No action required.
	LGBT Foundation	Yes. Could be clearer that those currently using oral PrEP with no problems aren't the key target for this treatment.	Comment noted. The population is intentionally kept broad to avoid excluding potentially eligible people. NICE will appraise cabotegravir within its marketing authorisation.
	NHIVNA	Agreed	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHSE	Yes See also responses to the 'Questions for consultation', below.	Comment noted. No action required.
	Terrence Higgins Trust	Defined as: People at high risk of acquiring sexually transmitted HIV-1. We feel this definition is too broad. Not all people at risk of HIV-1 will need CAB-LA. The majority of oral PrEP users i.e. gay, bisexual, and other men who has sex with men (GBMSM), take generic TD/FTC. It is well tolerated with high levels of acceptability. Adherence is generally good or adequate in the majority of these users. A small number of these people might require support with adherence or access to a long-acting injectable. A small number of GBMSM will have clinical indicators for TAF/FTC eligibility, due to reduction in renal function. A small number of these might benefit from access to a long-acting injectable. TAF/FTC might also be indicated for a small number of young adults and adolescents, due to bone mineral density. Some of these individuals might benefit from CAB-LA. But these will be comparatively small numbers and we don't foresee the need or desire for huge numbers of well-managed 'standard of care' oral PrEP users to migrate to CAB-LA.	Comments noted. The population is intentionally kept broad to avoid excluding potentially eligible people. NICE will appraise cabotegravir within its marketing authorisation.
	UK-CAB (joint response)	Whilst the broad definition is accurate in covering the population who *could* access Cabotegravir injectable for PrEP, we believe there are more specific circumstances in which it would be prescribed. The majority of current oral PrEP users find generic TD/FTC tolerable and acceptable.	Comments noted. The population is intentionally kept broad to avoid excluding potentially eligible people. NICE will appraise cabotegravir within its marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
	ViiV Healthcare	No, ViiV would like to suggest the scope to reflect the target population as explained in the remit section above: at-risk individuals for whom oral PrEP is not appropriate. ViiV would like to note [redacted] the proposed target population for this appraisal consists of individuals at risk of HIV infection for whom oral PrEP options are not appropriate. For these individuals there is an existing unmet need for a new additional PrEP modality such as cabotegravir which is expected to offer significant clinical benefit and to be cost-effective in this population.	Comments noted. The population is intentionally kept broad to avoid excluding potentially eligible people. NICE will appraise cabotegravir within its marketing authorisation.
Subgroups	BHIVA	1. Young people and adolescents: - Adolescents are particularly vulnerable to poor adherence to oral therapies, both for treatment and prevention.1.2 Long acting (LA) prevention is well established for contraception for adolescents with improved efficacy (pregnancy prevention) and user satisfaction when compared to daily oral trherapy.3,4 HIV PrEP studies have shown that even over 18 years, younger participants (18-25 years) have lower adherence to oral PrEP than older age groups.5 LA-cabotegravir (LA-CAB) has been shown to be safe, well tolerated with superior efficacy when compared to oral PrEP, due in the main to improved adherence.6,7 Further LA-CAB PrEP studies in adolescents are ongoing (NCT04692077, substudy of HPTN 083, NCT05937698, NCT05549726), with additional data on LA-CAB dosing, safety and tolerability from the MOCHA treatment study adding further reassurance.8 1) 2. People who use drugs	Comments noted. If evidence exists, subgroups of people at risk of sexually acquired HIV-1 infection for whom the technology might be particularly clinically effective or value for money will be considered.

Section	Consultee/ Commentator	Comments [sic]	Action
		- Associated problems such as mental health difficulties, homelessness, injecting use and multiple drug use, can all be expected to have a negative effect on the ability to adhere to daily oral medication. 2) 3. Sex workers - Particularly those who are more vulnerable affected by homelessness and drug use as above. 3) 4. Racially minoritized and other marginalised people - Through lower awareness of access to health services and the fact that sexual health care is free in the UK as well as other barriers such as English language skills. - There is a body of evidence from the USA that shows that Black American men who have sex with men and Transgender women have similar markers of behavioural risk but have higher HIV incidence. In the recent HPTN 083 study which demonstrated superiority of long acting cabotegravir vs oral TDF/FTC, HIV acquisition happened almost exclusively among Black and African American MSM, largely determined by lower adherence9. - Most studies of oral PrEP in cisgender women have been conducted in Sun-Saharan Africa, showing mixed results. Younger women have had particularly disappointing results with respect to PrEP efficacy. In these studies, PrEP choice and adherence have been identified as key issues that determine PrEP efficacy10. The HPTN 084 study comparing oral TDF/FTC vs long acting cabotegravir in women in Sub-Saharan Africa was a breakthrough study, showing very high levels of efficacy for cabotegravir in this population11. 5. People with contra-indications to both TDF/FTC and TAF/FTC e.g. people with very severe kidney disease with an eGFR <30.	

Section	Consultee/ Commentator	Comments [sic]	Action
	CHIVA	These subgroups should be identified based on incidence rate in UK demographics or risk characteristics rather than calling out specific communities And the challenge in meeting the UNAIDS 90-90-90 in children and young people (CYP) Young people have specific health and socioeconomic needs that differ from adult and are highly vulnerable with evidence of additional challenges in managing oral treatment and oral PrEP compared to adults. References: 1. Fonner VA, Ridgeway K, van der Straten A, Lorenzetti L, Dinh N, et al. Safety and efficacy of long-acting injectable cabotegravir as preexposure prophylaxis to prevent HIV acquisition. AIDS. 2023 May 1;37(6):957-966. doi: 10.1097/QAD.0000000000003494. Epub 2023 Jan 25. PMID: 36723489; PMCID: PMC10090368. 2. Yun K, Xu JJ, Zhang J, Li JM, Hu QH, Chu ZX, et al. Female and younger subjects have lower adherence in PrEP trials: a meta-analysis with implications for the uptake of PrEP service to prevent HIV. Sex Transm Infect. 2018 May;94(3):163-168. doi: 10.1136/sextrans-2017-053217. Epub 2017 Jul 29. PMID: 28756409. 3. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L,et al; HPTN 083 Study Team. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. N Engl J Med. 2021 Aug 12;385(7):595-608. doi: 10.1056/NEJMoa2101016. PMID: 34379922; PMCID: PMC8448593.	Comment noted. If evidence exists, subgroups of people at risk of sexually acquired HIV-1 infection for whom the technology might be particularly clinically effective or value for money will be considered.
	Gilead	• Gilead agrees that people at high risk of acquiring sexually transmitted HIV-1 are a key subgroup, which sits within the current or anticipated licensed populations. • Given the cost benefit of novel PrEP modalities is likely to be more impactful in specific populations, Gilead would suggest considering these, which might include:	Comment noted. If evidence exists, subgroups of people at risk of sexually acquired HIV-1 infection for whom the technology

Section	Consultee/ Commentator	Comments [sic]	Action
		○ Those unable to routinely access sexual health services and thus oral PrEP ○ Those who may meet the clinical exclusion criteria for use of emtricitabine and tenofovir disoproxil (FTC/TDx) ○ Those who may not be able to adhere to an oral PrEP regimen, such that it may not provide adequate protection against HIV acquisition. Barriers may be at individual (fear of HIV, fear of side effects, and PrEP characteristics), interpersonal (parental influence, absence of a sexual partner), community (peer influence, social stigma), institutional (long waiting times at clinics, attitudes of health workers), and structural (mode of administration, accessibility concerns) levels (Young I, Flowers P, McDaid LD. BMJ Open. 2014 Nov 20;4(11):e005717; Muhumuza R et al. Arch Sex Behav. 2021; 50(4): 1729–1742) Whilst Gilead notes that the likely indication for cabotegravir for PrEP will be for those at high risk of sexually acquired HIV, this population is not the only one at high risk of acquiring HIV, and so consideration should be given to the role of novel injectables in preventing non-sexual acquisition of HIV in people who inject drugs. This could support wider global and UK government ambitions of getting to zero HIV transmission by 2030	might be particularly clinically effective or value for money will be considered.
	HIVPA	HIVPA suggest that this evaluation mirrors the US marketing authorisation and considers use those in those over 12, rather than 18, with the wording this for adults and adolescents 35kg and over. The pharmacokinetic data support this use and this will ensure this important group is not overlooked and access isn't compromised.	Comment noted. NICE will appraise cabotegravir within its UK marketing authorisation.
	LGBT Foundation	- Those who cannot currently access oral PrEP or who are unable to adhere appropriately to their current dosing regime.	Comment noted. If evidence exists, subgroups of people at

Section	Consultee/ Commentator	Comments [sic]	Action
		- Groups mentioned above: homeless populations, sex workers, migrants trans people, those at risk of violence or abuse	risk of sexually acquired HIV-1 infection for whom the technology might be particularly clinically effective or value for money will be considered.
	NHIVNA	• Young people as it will affect the bone density in the still developing body • Older women (peri-menopausal) as they have increased risk of osteoporosis and CVD • Women who want to get pregnant as cabotegravir has not been widely trialed during pregnancy and breastfeeding - first evidence from HTPN 084 have not become available yet • Drug using adults for considerations related with adherence and DDIs • People suffering stigma and self-stigma as the medication provides discretion • People in abusive relationships as the medication provides discretion • People who live in shared accommodation and don't want to disclose their sexual risk as the medication provides discretion • People struggling with adherence to oral PrEP (including mental health struggles, adherence, etc.) • People who are homeless • People employed in sex work	Comment noted. If evidence exists, subgroups of people at risk of sexually acquired HIV-1 infection for whom the technology might be particularly clinically effective or value for money will be considered.
	NHSE	Since the HPTN trials demonstrated particular benefit of IM-CAB for women, and there are very few women on PrEP in England, women should be considered as a subgroup (with the caveat that a low absolute risk may render IM-CAB not cost-effective)	Comment noted. If evidence exists, subgroups of people at risk of sexually acquired HIV-1 infection for

Section	Consultee/ Commentator	Comments [sic]	Action
			whom the technology might be particularly clinically effective or value for money will be considered.
	Terrence Higgins Trust	Some people belonging to one or more of these groups might be more likely to find CAB-LA a better choice, or the only PrEP option suitable and effective for them: • Female sex workers • Black African heterosexuals • People under 25 • People experiencing homelessness • People with substance misuse • People from minority ethnic groups • People experiencing domestic abuse/intimate partner violence • People accessing reproductive health and unplanned pregnancy services • Recent migrants	Comment noted. If evidence exists, subgroups of people at risk of sexually acquired HIV-1 infection for whom the technology might be particularly clinically effective or value for money will be considered.
	UK-CAB (joint response)	The appraisal should consider People at high risk of acquiring sexually transmitted HIV-1, and more specifically those who cannot currently access oral-based PrEP (e.g. TD/FTC etc.), or who not find it acceptable in their current circumstances. Populations may include but not be limited to the following groups. People who decline pill-based interventions due to potential violence, abuse, or being incorrectly assumed to be living with HIV e.g.:	Comment noted. If evidence exists, subgroups of people at risk of sexually acquired HIV-1 infection for whom the technology might be particularly clinically effective or

Section	Consultee/ Commentator	Comments [sic]	Action
		• Sex workers (in particular sex workers with heterosexual clients, who are likely to have less knowledge of HIV prevention interventions) • Young people and adolescents, in particular those living with family or in shared student accommodation • People experiencing domestic abuse/intimate partner violence • People living in other shared accommodation, e.g. refuges, shelters, asylum and refugee accommodation, shared housing due to limited income or poverty. Groups more likely to want to utilise a more discreet HIV prevention intervention, due to HIV-associated stigma, or discretion around their sexual behaviours and partners, e.g.: • People at high risk of HIV having sex outside of a monogamous relationship • Black African heterosexuals People who travel regularly: • People working in countries which prohibit people with HIV from entering/working • People requiring discretion when visiting other countries for personal reasons (e.g. visiting partners, family etc.) Clinical considerations: • People at high-risk of acquiring HIV who experience Dysphagia (unable to swallow pills and tablets) • People at high-risk of acquiring HIV who live with multi-morbidities, taking large numbers of pill-based medications, who could benefit	value for money will be considered.

Section	Consultee/ Commentator	Comments [sic]	Action
		from a reduction in pill-burden whilst protecting themselves from HIV, e.g. older gay and bisexual men. Other groups may include: • People accessing reproductive health and unplanned pregnancy services who require discretion around their sexual and reproductive health needs	
	ViiV Healthcare	No relevant subgroups were identified.	Comment noted. No action required.
Comparators	BHIVA	Yes. It's important to understand that tenofovir is available as two pro-drugs – disproxil fumarate and alafenamide, the former being generic and the latter proprietary. However, the main issue for this comparison is difference in formulation and the potential benefits.	Comment noted. The comparators have been updated to include tenofovir disoproxil or alafenamide in combination with emtricitabine.
	CHIVA	Yes	Comment noted. No action required.
	Gilead	Gilead would suggest including Descovy (emtricitabine 200mg/tenofovir alafenamide 25mg tablets) as a relevant comparator • Descovy is licensed by the MHRA and is indicated for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in at-risk men who have sex with men, including adolescents (with body weight at least 35 kg) (SmPC via https://www.medicines.org.uk/emc/product/2108).	Comment noted. The comparators have been updated to include tenofovir disoproxil or alafenamide in combination with emtricitabine.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Descovy is reimbursed within England by NHS-England within the *Clinical Commissioning Policy Reimbursement for the use of generic and second line drugs for Pre Exposure Prophylaxis (PrEP) for the prevention of HIV (2112) [230402P]* available via https://www.england.nhs.uk/publication/reimbursement-for-the-use-of-generic-drugs-for-pre-exposure-prophylaxis-prep-for-the-prevention-of-hiv/ • Within this NHS-E policy, the use of Descovy is funded broadly where there are certain clinical indications to avoid emtricitabine/tenofovir disoproxil, which may also be relevant to the positioning of cabotegravir for PrEP. Gilead would suggest TDx as a single agent is not a suitable comparator. TDx has not been licensed by any major regulator for the prevention of HIV, and while we acknowledge there are data, these may not be supportive of its use or inclusion as a comparator for PrEP in a UK setting Gilead believe that oral comparators e.g. Descovy or FTC/TDx do not fully encompass the benefits for injectable PrEP versus oral, and the populations who may benefit from PrEP but are not able to access it should be considered (see Gilead's comment in 'subgroups' above)	Off-label and unlicensed treatments are not automatically excluded as comparators. The company can make a case for which comparators are appropriate in their submission.
	HIVPA	Tenofovir alafenamide with emtricitabine is now commissioned as a second line agent for pre-exposure prophylaxis. HIVPA suggest that this is also considered a since cabotegravir is likely to be a second line option due to cost of the drug and healthcare staff to deliver. Tenofovir alone is listed as a comparator however, this isn't used in clinical practice as it does not provide adequate protection,	Comment noted. The comparators have been updated to include tenofovir disoproxil or alafenamide in combination with emtricitabine. Off-label and unlicensed

Section	Consultee/ Commentator	Comments [sic]	Action
			treatments are not automatically excluded as comparators. The company can make a case for which comparators are appropriate in their submission.
	LGBT Foundation	We believe comparators as listed in the documents to be complete and appropriate.	Comment noted. No action required.
	NHIVNA	Descovy should also be included in the consultation as it addresses the needs of people with renal or bone considerations and is also licenced as PrEP and the treatment of Hepatitis B infection	Comment noted. The comparators have been updated to include tenofovir disoproxil or alafenamide in combination with emtricitabine.
	NHSE	The statement in the draft scope *Established clinical management including tenofovir alone or in combination with emtricitabine* is incorrect. Established clinical management is: First line: tenofovir disoproxil in combination with emtricitabine Second line: tenofovir alafenamide in combination with emtricitabine	Comment noted. The comparators have been updated to include tenofovir disoproxil or alafenamide in combination with emtricitabine. Off-label and unlicensed treatments are not automatically excluded

Section	Consultee/ Commentator	Comments [sic]	Action
		As per NHS England commissioning policy Reimbursement for the use of generic and second line drugs for Pre Exposure Prophylaxis (PrEP) for the prevention of HIV (2112) [230402P] (england.nhs.uk)	as comparators. The company can make a case for which comparators are appropriate in their submission.
	Terrence Higgins Trust	Defined as: Established clinical management including tenofovir alone or in combination with emtricitabine To our knowledge, all people accessing PrEP through the NHS are offered generic TD/FTC (combined). TD (or tenofivir alone) is not prescribed, but is referenced in the current BASHH BHIVA PrEP Guidelines for use in 'heterosexual men and women'. ***"We recommend that TDF alone can be offered to heterosexual men and women where FTC is contraindicated. (1A)"*** TAF/FTC is likely to qualify as a relevant comparator. https://www.bhiva.org/file/5b729cd592060/2018-PrEP-Guidelines.pdf **3 Summary of recommendations** **4.1 Evidence for safety and efficacy in men who have sex with men (MSM): recommendations**	Comment noted. The comparators have been updated to include tenofovir disoproxil or alafenamide in combination with emtricitabine. Off-label and unlicensed treatments are not automatically excluded as comparators. The company can make a case for which comparators are appropriate in their submission.

Section	Consultee/ Commentator	Comments [sic]	Action
		1. We recommend that PrEP with on-demand or daily oral TD-FTC should be offered to HIV-negative MSM who are identified as being at elevated risk of HIV acquisition through condomless anal sex in the previous 6 months and ongoing condomless anal sex. (1A) 2. We recommend that PrEP with on-demand or daily oral TD-FTC should be offered to HIV-negative MSM having condomless anal sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A) 3. We suggest that tenofovir alone should not currently be offered as PrEP to MSM. This recommendation is based on lack of evidence, rather than evidence of lack of effect. (2C) **Good practice point** • Consider PrEP on a case by case basis in MSM with current factors other than condomless anal sex in previous 6 months that may put them at increased risk of HIV acquisition. See Section 5. **4.2 Evidence for safety and efficacy in heterosexual populations: recommendations** 4. We recommend that daily oral TD-FTC should be offered to HIV-negative heterosexual men and women having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A)	

Section	Consultee/ Commentator	Comments [sic]	Action
		5. We suggest that PrEP with daily oral TD-FTC should be offered on a case-by-case basis to heterosexual men and women with current factors that may put them at increased risk of HIV acquisition. See Section 5.1. (2B) 6. We recommend that TDF alone can be offered to heterosexual men and women where FTC is contraindicated. (1A)	
	UK-CAB (joint response)	Our understanding is that the vast majority of people accessing PrEP in England and Wales are prescribed TD/FTC. As of May 2023, F/TAF is also available as an alternative PrEP intervention for people with pre-existing bone or kidney disease (estimated to be 400-700 people), this group of people could also potentially benefit from access to Cabotegravir Injectable. We suggest TD/FTC and F/TAF are suitable comparators.	Comment noted. The comparators have been updated to include tenofovir disoproxil or alafenamide in combination with emtricitabine.
	ViiV Healthcare	ViiV suggests the removal of TDF monotherapy from the comparators list. *Justification:* single agent TDF is not currently licensed for PrEP, but can only be considered as part of the BHIVA/BASHH guidelines as an alternative for heterosexual men and women, and this population likely represents a small proportion of PrEP use in England and Wales. Furthermore, only tenofovir in combination with emtricitabine is reimbursed by the specialised clinical commissioning policy for PrEP.[6] The appropriate comparators for this appraisal are:	Comment noted. The comparators have been updated to include tenofovir disoproxil or alafenamide in combination with emtricitabine. Off-label and unlicensed treatments are not

Section	Consultee/ Commentator	Comments [sic]	Action
		- Tenofovir in combination with emtricitabine or - No PrEP for people for whom oral PrEP options are not appropriate	automatically excluded as comparators. The company can make a case for which comparators are appropriate in their submission.
Outcomes	BHIVA	Yes	Comment noted. No action required.
	CHIVA	Yes! though would also emphasise the importance of qualitative data based on patient related outcomes and stigma-related health outcomes	Comment noted. The committee will consider all relevant qualitative outcomes during the appraisal.
	Gilead	We would suggest the following as outcome measures: **Impact on clinical services:** • The impact on clinical services of a Q2 monthly injection on sexual health services, which may be stretched should be considered, compared to current SOC • Gilead notes from the patient information leaflet (PIL) of the current licensed Vocabria (cabotegravir for HIV treatment), and the USPI of Apretude that it requires administration by a health care professional using a specific technique • For Vocabria for treatment, if a person misses their scheduled dose by more than 7 days this may require action. If the GB SMPC reflects the	Comment noted. The outcomes listed are not exhaustive and the committee will consider all relevant costs and benefits during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		US label, this may include oral pills for a period. This may be impacted by travel, particularly in a highly mobile younger population who may benefit from PrEP **Equity of access to PrEP** • Gilead recognises that certain groups at risk of HIV may not be able to access oral PrEP for a variety of reasons, as outlined in the Government HIV Action Plan. • Including an analysis of those whom injectable PrEP could enable better access to HIV prevention measures could support the 2030 goal of zero HIV transmissions. **Proportion with HIV resistance mutations on PrEP failure, and impact on recommend first line ART** • Within the US DHHS guidelines (where cabotegravir for PrEP is licensed), selection of first line ART for treatment of HIV is actively influenced by prior use of CAB-LA for PrEP • *For people with HIV and a history of using CAB-LA as PrEP, INSTI genotypic resistance testing should be done before the start of ART. If treatment is begun prior to results of genotypic testing, the following regimen is recommended: Boosted darunavir plus (TAF or TDF) plus (FTC or 3TC)—pending the results of the genotype test (AIII)* • Within the registrational studies for cabotegravir for PrEP (HPTN 083 and HPTN 084), INSTI resistance associated mutations where observed in 4/12 participants with incident HIV infection in HPTN 083 (vs 4/39 taking FTC/TDF), and 0/3 within HPTN 084 (vs 1/36 taking FTC/TDF)	

Section	Consultee/ Commentator	Comments [sic]	Action
		• INSTI resistance testing at baseline is not currently routinely recommended by the BHIVA HIV-1 treatment guidelines, and so the introduction of a INSTI based PrEP option may have impact on these, as well as associated costs of INSTI resistance testing. • We would therefore suggest evaluating the clinical and costs implications on the first line management of HIV-1, including impact on choice of HIV treatment regimens which may not be one of the prefered regimens for most people with HIV according to the BHIVA HIV-1 treatment guidelines 2022.	
	HIVPA	None	No action required.
	LGBT Foundation	Yes	Comment noted. No action required.
	NHIVNA	Agreed	Comment noted. No action required.
	NHSE	The outcome measures to be considered are appropriate; in addition we propose the following are included: • Adherence • Visit frequency • Monitoring requirements • Self-reported stigma	Comments noted. The outcome section of the scope has been updated.
	Terrence Higgins Trust	Yes. Additional suggestions:	Comment noted. The outcome section of the

Section	Consultee/ Commentator	Comments [sic]	Action
		• The implications of missing injection appointments and the evidence for bridging on oral cabotegravir. CAB/RPV BHIVA HIV Treatment guidelines: https://www.bhiva.org/file/63513a1745ea9/BHIVA-guidelines-on-antiretroviral-treatment-for-adults-living-with-HIV-1-2022.pdf *"Adherence is critical with a maximum +/– 7-day window for early/late administration; oral bridging can be used but should be considered an exception rather than routine."* • Diagnostics required for CAB-LA: ***Monitoring on injectable cabotegravir*** • *FDA and CDC guidance is to conduct an RNA viral load test together with an HIV antigen-antibody test every 8 weeks. This is based on the 62 day delay in diagnosis observed in HPTN083[3] when HIV RNA testing was not conducted in real-time. Incident infections in adherent users of long-acting cabotegravir were very infrequent in the clinical trials, but RNA testing (plus HIV antigen-antibody test) on the day of the switch is recommended. Other tests recommended when starting oral PrEP in the UK (see chapter 6) should also be conducted, although there is no evidence from clinical trials to suggest that ongoing routine renal or hepatic monitoring is indicated.* • *Long-acting cabotegravir users who have only had one injection, or whose due injection was over 8 weeks late, need special*	scope has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		consideration regarding the possibility of continuing long-acting cabotegravir in the UK. In HPTN 083 and 084, participants who were 8 or more weeks late for an injection restarted with a 4 week interval between the first two injections before moving to an 8 week interval. A 12 week interval between the first two injections and a 16 week interval for the third and later injections was tolerated in the trial. However, FDA guidance is more conservative and recommends restarting for users who are 4 or more weeks late (allowing a gap of up to 8 weeks between the first two injections, or up to 12 weeks for the third and later). This is the approach recommended in the UK, including RNA testing in addition to an HIV antigen-antibody test at each visit to minimise the risk of delay in diagnosis and consequent integrase inhibitor resistance mutations. • *Contraindications: There are a number of drug interactions to consider when prescribing LA-CAB, notably anticonvulsants and antibiotics for tuberculosis* Thoughts on • The implications of missing injection appointments and the evidence for bridging on oral cabotegravir. CAB/RPV BHIVA HIV Treatment guidelines: https://www.bhiva.org/file/63513a1745ea9/BHIVA-guidelines-on-antiretroviral-treatment-for-adults-living-with-HIV-1-2022.pdf	

Section	Consultee/ Commentator	Comments [sic]	Action
		Adherence is critical with a maximum +/– 7-day window for early/late administration; oral bridging can be used but should be considered an exception rather than routine. • Diagnostics required for CAB_LA VL: **9.3 Monitoring on injectable cabotegravir** • FDA and CDC guidance is to conduct an RNA viral load test together with an HIV antigen-antibody test every 8 weeks. This is based on the 62 day delay in diagnosis observed in HPTN0833 when HIV RNA testing was not conducted in real-time. Incident infections in adherent users of long-acting cabotegravir were very infrequent in the clinical trials, but RNA testing (plus HIV antigen-antibody test) on the day of the switch is recommended. Other tests recommended when starting oral PrEP in the UK (see chapter 6) should also be conducted, although there is no evidence from clinical trials to suggest that ongoing routine renal or hepatic monitoring is indicated. • Long-acting cabotegravir users who have only had one injection, or whose due injection was over 8 weeks late, need special consideration regarding the possibility of continuing long-acting cabotegravir in the UK. In HPTN 083 and 084, participants who were 8 or more weeks late for an injection restarted with a 4 week interval between the first two injections before moving to an 8 week interval. A 12 week interval between the first two injections and a 16 week interval for the third and later injections was tolerated in the trial. However, FDA guidance is more conservative and recommends restarting for users who are 4 or more weeks late (allowing a gap of up to 8 weeks between the first two	

Section	Consultee/ Commentator	Comments [sic]	Action
		injections, or up to 12 weeks for the third and later). This is the approach recommended in the UK, including RNA testing in addition to an HIV antigen-antibody test at each visit to minimise the risk of delay in diagnosis and consequent integrase inhibitor resistance mutations. • Contraindications: There are a number of drug interactions to consider when prescribing LA-CAB, notably anticonvulsants and antibiotics for tuberculosis	
	UK-CAB (joint response)	The outcomes are appropriate. 'Health-related quality of life' should factor mental wellbeing and psychosexual issues – for example removing the fear and anxiety of acquiring HIV during sex for people at high-risk of acquiring HIV.	Comment noted. The committee will consider all relevant health-related quality of life outcomes when appraising the technology.
	ViiV Healthcare	Yes, ViiV healthcare agrees with the proposed outcome measures	Comment noted. No action required.
Equality	BHIVA	None	No action required.
	CHIVA	No comment	No action required.
	Gilead	HIV-1 disproportionately affects some populations such as gay, bisexual and trans people, people of black African family background, people from countries with a high community prevalence, people who are homeless, and people who inject drugs. Gilead believe all of these populations and communities should have equitable access to PrEP.	Comment noted. The committee will consider equalities issues during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
	HIVPA	See above re adolescents and age. There is also valuable for those who cannot take oral pre-exposure prophylaxis for any reason, particularly those where confidentiality is compromised	Comment noted. The committee will consider equalities issues during the appraisal.
	LGBT Foundation	N/A	No action required.
	NHIVNA	We feel the bellow charities represent marginalised populations, disproportionally affected by HIV. At the same time, better geographic representation could be achieved by involving some of the following. <u>PrEP charities</u> PrEPster <u>HIV Charities</u> Positive East George House Trust - Manchester Sahir House - Liverpool Metro Charity Sussex Beacon - Brighton Waverley care - Scotland	Comment noted. Most of these organisations have been added to the stakeholder list. Only UK national organisations can be included in the stakeholder list.

Section	Consultee/ Commentator	Comments [sic]	Action
		<u>Drugs and addiction charities</u> Scottish Drugs Forum Antidote: Drug and Alcohol support Turning Point Change Grow Live <u>Trans charities</u> Stonewall Mermaids <u>Sex Worker Charities</u> Red umbrella	
	NHSE	This intervention will be administered in a healthcare setting, so from a practical perspective may make it more difficult for people with a disability, caring responsibilities or another protected characteristic that can potentially lead an individual to find it more challenging to visit a healthcare setting in person.	Comment noted. The committee will consider equalities issues during the appraisal.
	Terrence Higgins Trust	From both an equity and equalities perspective, in regards to HIV PrEP options, CAB-LA appears to be both effective and have high acceptability in women, and could potentially address the inequalities caused by disparities in effectiveness of oral PrEP in women compared with men who have sex with men (MSM).	Comment noted. The committee will consider consideration of equalities issues during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		CAB-LA has the potential to be revolutionary for adolescent girls and young women in sub-Saharan Africa who are disproportionately affected by HIV, and for women in other parts of the world including high income countries with low PrEP uptake in women. CAB-LA could also address huge disparities in PrEP uptake across populations and subpopulations including female sex workers, Black African heterosexuals, people under 25, people experiencing homelessness, people with substance misuse, people from minority ethnic groups, people experiencing domestic abuse/intimate partner violence, people accessing reproductive healthcare and unplanned pregnancy services, and recent migrants. CAB-LA could remove barriers to access for women and subpopulations who don't visit sexual health clinics with the same frequency as gay and bisexual men, instead preferring to get their sexual and reproductive health through their GP/family doctor; which in itself made PrEP, in practice, inaccessible to those people. CAB-LA can address equity and barriers to access by challenging the current provision model/technology.	
	UK-CAB (joint response)	Clarification on the definition of 'young people' from NICE would be appreciated for us to fully assess the impact of this appraisal on 'non-adults'.	Comment noted. NICE will appraise cabotegravir within its UK marketing authorisation. The age the technology is indicated in will be specified in the

Section	Consultee/ Commentator	Comments [sic]	Action
			summary of product characteristics.
	ViiV Healthcare	PrEP is a key component of HIV prevention. While UK individuals currently have access to oral PrEP through the NHS there are still some identifiable disproportionately vulnerable groups who are unable to benefit from oral PrEP and for whom there is an unmet need for new PrEP modalities. These groups may include, but are not limited to, gender diverse populations and ethnic minorities. A more detailed description of these groups is provided in the response to the questions for consultation section.	Comments noted. The committee will consider equalities issues during the appraisal.
Other considerations	BHIVA	**Where do you consider cabotegravir injections will fit into the existing care pathway for pre-exposure prophylaxis of HIV-1?** - Given the relative costs and high efficacy of oral tenofovir/emtricitabine (TDF/FTC) it is likely that cabotegravir injections would be a second line option in people where TDF/FTC is likely to be less effective or where there are safety concerns with both TDF/FTC and tenofovir alafenamide/emtricitabine (TAF/FTC). **Would cabotegravir injections be a candidate for managed access?** - Yes. This arrangement would help to understand the cost-effectiveness in people who are less able to use TDF/FTC effectively as well as helping to understand how the healthcare system can best deliver tis technology. **Do you consider that the use of cabotegravir injections can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** - No comment	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all relevant comparators for cabotegravir injections been included in the scope? - Yes. It's important to understand that tenofovir is available as two pro-drugs – disproxil fumarate and alafenamide, the former being generic and the latter proprietary. However, the main issue for this comparison is difference in formulation and the potential benefits. **In what situations is cabotegravir expected to be used in clinical practice? For example, are cabotegravir injections expected to be used in place of oral PrEP?** - Cabotegravir injections would likely be used in people who have particular vulnerabilities or other needs that make the use of oral PrEP less effective. These would be people who have difficulty adhering to oral PrEP, but are at significant risk of HIV or particular sub-populations who have experienced less protection from oral PrEP in clinical studies. The determinants of lower PrEP efficacy are generally those that affect ability to adhere. These would include structural and other barriers to engagement in healthcare as well as psychological and social challenges making these individuals more vulnerable. **Will cabotegravir injections need to be administered in healthcare settings?** - Likely in the first instance. However, IM injections can be administered in the community and cabotegravir does not require refrigeration, making it quite suitable for delivery in service models that would improve access to those who are currently less well engaged in HIV prevention services. - Specific groups such as youth should be consulted about preferred delivery settings.	

Section	Consultee/ Commentator	Comments [sic]	Action
		How do patients and clinicians determine a person's level of risk for acquiring HIV-1? 1) Sexual history – condomless sex with frequent partner change. Men who have sex with men and transgender identity. 2) Recent bacterial STI, especially if rectal infection or infectious syphilis. 3) Other markers of risk, e.g. sexual exploitation, intimate partner violence, commercial sex work. 4) Wider determinants of health: e.g. member of racially minoritized community, recent migrant. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Data are available from the primary outcomes of large randomised controlled trials, their open label extensions and sub-studies. There are also data available from PrEP implementation and demonstration projects. Studies would include, though not limited to: iPrEX and iPrEX OLE, PROUD, iPERGAY, Prevenir, HPTN 083, HPTN 084, Partners PrEP, the VOICE trial. Some references are provided below. We can provide more if required. **References** 1. Foster C, Ayers S, Fidler S. Antiretroviral adherence for Adolescents living with HIV; drug delivery and forgiveness. *Ther Adv Inf Dis* 2020 May 7;7:2049936120920177. 2. Can we improve adolescent adherence? Drug Ther Bull. 2016 Jan;54(1):6-9. doi: 10.1136/dtb.2016.1.0375. PMID: 26763597. 3. Farah D, Andrade TRM, Di Bella ZIKJ, Girão MJBC, Fonseca MCM. Current evidence of contraceptive uptake, pregnancy and continuation rates in young women: a systematic review and Meta-analysis. Eur J Contracept Reprod Health Care. 2020 Dec;25(6):492-501. 4. Todd N, Black A. Contraception for Adolescents. J Clin Res Pediatr Endocrinol. 2020 Feb 6;12(Suppl 1):28-40. doi:	

Section	Consultee/ Commentator	Comments [sic]	Action
		10.4274/jcrpe.galenos.2019.2019.S0003. PMID: 32041390; PMCID: PMC7053440. 5. Yun K, Xu JJ, Zhang J, Li JM, Hu QH, Chu ZX, et al. Female and younger subjects have lower adherence in PrEP trials: a meta-analysis with implications for the uptake of PrEP service to prevent HIV. Sex Transm Infect. 2018 May;94(3):163-168. doi: 10.1136/sextrans-2017-053217. Epub 2017 Jul 29. PMID: 28756409. 6. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L,et al; HPTN 083 Study Team. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. N Engl J Med. 2021 Aug 12;385(7):595-608. doi: 10.1056/NEJMoa2101016. PMID: 34379922; PMCID: PMC8448593. 7. Fonner VA, Ridgeway K, van der Straten A, Lorenzetti L, Dinh N, et al. Safety and efficacy of long-acting injectable cabotegravir as preexposure prophylaxis to prevent HIV acquisition. AIDS. 2023 May 1;37(6):957-966. doi: 10.1097/QAD.0000000000003494. Epub 2023 Jan 25. PMID: 36723489; PMCID: PMC10090368. 8. Bolton Moore C, Capparelli E, Calabrese K, Best B, Ward C et al. Safety and PK of long acting cabotegravir and rilpivirine. CROI 2022 February 12-16, Virtual: P00738. 9. Scott H, Hanscom B, Hutchinson C et al. CABOTEGRAVIR FOR HIV PrEP IN US BLACK MEN AND TRANSGENDER WOMEN WHO HAVE SEX WITH MEN. CROI conference 2023. Abs O161 10. Marrazzo J, Becker M, Bekker L-G et al. 8+ years pooled analysis: adherence and HIV incidence in 6000 women on F/TDF for PrEP. 11. Delany-Moretlwe S, Hughes JP, Bock P et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet 2022. May 7;399(10337):1779-1789	
	CHIVA	No comment	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Gilead	None	No action required.
	HIVPA	None	No action required.
	LGBT Foundation	N/A	No action required.
	NHIVNA	Viral load testing will be required for people who are on cabotegravir PrEP at every visit (latest every 3 months) due to LEVI Syndrome – this could have an additional cost for the NHS and the patients need to be informed of the monitoring requirements	Comment noted. The outcome section of the scope has been updated.
	NHSE	None	No action required.
	Terrence Higgins Trust	na	No action required.
	UK-CAB (joint response)	None	No action required.
	ViiV Healthcare	**No prior NICE HIV-1 PrEP appraisal** ViiV knows of no known NICE precedent in relation to HIV-1 prevention appraisals, which could make this appraisal more complicated. However, current available PrEP options, evaluated and reimbursed via specialised commissioning depend on the BHIVA/BASHH guidelines which outline the current standard of care. **Appropriate terminology** ViiV would like to indicate that a similar approach as the one described in the BHIVA guidelines to naming groups and individuals should be followed	Comments noted. The technology will be appraised in line with NICE's health technology evaluations: interim methods and process guide. The committee will consider equalities issues during

Section	Consultee/ Commentator	Comments [sic]	Action
		throughout the appraisal process to ensure that consistent and appropriate denomination is used to promote equality and avoid risk of discrimination. As stated in the BHIVA Inclusivity statement, it is critical to recognise that guidelines and recommendations in the context of HIV should be inclusive and relevant to all, regardless of sexuality or gender identity or expression. The BHIVA guidelines indicate that phrases such as 'men who have sex with men' refer to cis-gender or non-binary or gender-queer men who have sex with men and 'heterosexual men and women' refers to cis-gender or non-binary or gender-queer men and women who have heterosexual sex. Where sections are specifically relevant to trans people, the BHIVA guidelines identify this using the terms trans people, trans men, or trans women. **Oral tablets for lead-in or bridging** ViiV would like to add that optional oral cabotegravir tablets may be considered by clinicians. [redacted]	the appraisal. NICE will appraise cabotegravir within its marketing authorisation.
Questions for consultation	BHIVA	None	No action required.
	CHIVA	In reference to consultation questions, given the caution around treating, similar to apply to prevention; additionally need to balance with service capacity; **Clinical practice use:** instead of oral prep where people have concerns or issues with taking tablets for whatever reason, alongside depot contraception;	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Healthcare settings Yes! given the specific site needed to inject it but would be important to consider having community healthcare settings trained esp given needs and flexibility for young people; **Person's level of risk** determined by risks for HIV reference PrEP and PEP guidelines (BHIVA, BASSH) and practical assessment of the risk factors based on patient and clinical considerations/judgement.	
	Gilead	None	No action required.
	HIVPA	Questions for consultation Where do you consider cabotegravir injections will fit into the existing care pathway for pre-exposure prophylaxis of HIV-1? As a second line option for those who cannot take tenofovir disoproxil due to contraindications or those who cannot take any oral pre-exposure due to difficulties with adherence or disclosure. Those unable to tolerate oral PrEP Those with eGFR below license for tenofovir alafenamide/emtricitabine PrEP <30 ml/min Those with swallowing issues or unable to tolerate oral dosage forms Those who oral PrEP risks inadvertent disclosure of sexual activity or those who cannot safely negotiate daily access to oral prep due to vulnerability/safeguarding issues. Would cabotegravir injections be a candidate for managed access? Yes	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of cabotegravir injections can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Addressed above Have all relevant comparators for cabotegravir injections been included in the scope? See above comments regarding tenofovir alafenamide Are the outcomes listed appropriate? Yes Are there any subgroups of people in whom cabotegravir is expected to be more clinically effective and cost effective or other groups that should be examined separately? See above re vulnerable populations In what situations is cabotegravir expected to be used in clinical practice? For example, are cabotegravir injections expected to be used in place of oral PrEP? Where there is a perceived benefit, eg. Adherence of confidentiality concerns. Will cabotegravir injections need to be administered in healthcare settings? Yes, this is a deep intramuscular injection	
	LGBT Foundation	How do patients and clinicians determine a person's level of risk for acquiring HIV-1? Usual clinical indicators for PrEP prescription include repeat PEPSE prescriptions, repeat STI diagnoses, having unprotected sex with partners of unknown HIV status or with a detectable viral load.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHIVNA	See below	No action required.
	NHSE	Where do you consider cabotegravir injections will fit into the existing care pathway for pre-exposure prophylaxis of HIV-1? *As an option for individuals at high risk of HIV in whom alternative therapies are inappropriate/contraindicated./lead to increased stigma. Currently available PrEP medicinal therapies are all oral and comprised of a tenofovir component.* Would cabotegravir injections be a candidate for managed access? *No* Do you consider that the use of cabotegravir injections can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? *We have been unable to respond to this question without further information on the QALYs that are being used in the calculation. The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.* Have all relevant comparators for cabotegravir injections been included in the scope? *CAB has been trialled against TDF components only, there are no data available re TAF vs CAB PrEP.* Are the outcomes listed appropriate? *See 'Outcomes' section in table (above)*	Comment noted. No action required. See previous responses above regarding suggestion of including cis women as a subgroup.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are there any subgroups of people in whom cabotegravir is expected to be more clinically effective and cost effective or other groups that should be examined separately? *CAB PrEP has data in cis-women, multiple ethnicities but as per the TAF PrEP application may not encompass the groups in whom it will be used most-those with renal/bone/adherence/stigma issues. For the reasons outlined above, cis women could be analysed as a subgroup.* In what situations is cabotegravir expected to be used in clinical practice? For example, are cabotegravir injections expected to be used in place of oral PrEP? *Likely to be recommended in individuals for whom standard of care TDF/FTC PrEP or current second line therapy tenofovir alafenamide (TAF)/FTC PrEP is inappropriate/contraindicated, those with adherence issue, stigma thus increasing access to PrEP in individuals at high risk of HIV acquisition.* Will cabotegravir injections need to be administered in healthcare settings? *Yes, currently* How do patients and clinicians determine a person's level of risk for acquiring HIV-1? *This is challenging for all populations beyond gay, bisexual and other men who have sex with men (GBMSM). Current BHIVA/BASHH guidance provides more specific risk stratification parameters for GBMSM, based on UKHSA data. It is very challenging to identify who amongst other groups, e.g. cis women, is at high risk of HIV acquisition.* Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Large RCTS available HPTN 077/ 083/084. CAB superior to TDF/FTC and trials stopped early. *Landovitz RJ, Li S, Eron Jr JJ, et al. Tail-phase safety, tolerability, and pharmacokinetics of longacting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. The Lancet HIV. 2020; Landovitz RJ, et al. N Engl J Med 2021;385:595–608; Delany-Moretlwe S, et al. Lancet 2022;399:1779–89* *Already in multiple guidelines internationally-DHHS, WHO, IAS*	
	Terrence Higgins Trust	**Where do you consider cabotegravir injections will fit into the existing care pathway for pre-exposure prophylaxis of HIV-1?** We don't consider it optimum or equitable for CAB-LA to ***only*** fit into existing pathways for HIV PrEP. While we think it should be available in specialist sexual health services and offered opportunistically to eligible individuals and through specialist clinics, for example, clinics specifically for female sex workers or in certain trans clinics. It must also be made available in other services already used by women and other people who are currently underserved in HIV prevention efforts, who might have an elevated risk of acquiring HIV, and who would benefit from PrEP. GP surgeries and community pharmacies in areas with the highest HIV prevalence should hold stock of CAB-LA or be able to order it in on a fast track system. Information giving and signposting should be considered in services which support • People under 25	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		• People experiencing homelessness • People with substance misuse • People from minority ethnic groups • People experiencing domestic abuse/intimate partner violence • People accessing reproductive health and unplanned pregnancy services • Recent migrants Where feasible, these services should offer CAB-LA on-site. The process of commissioning such services is likely to be protracted. In the interim, implementation studies should be conducted with the aim of providing access to this technology in the shortest time possible **Would cabotegravir injections be a candidate for managed access?** If concurrent with usual routine commissioning processes, yes. **Have all relevant comparators for cabotegravir injections been included in the scope?** TAF/FTC added as a suggestion **Will cabotegravir injections need to be administered in healthcare settings?** Initially yes – self-administered feasibility is being researched REF https://www.aidsmap.com/news/aug-2022/new-formulations-and-alternative-injection-sites-might-allow-self-administration-long **How do patients and clinicians determine a person's level of risk for acquiring HIV-1?**	

Section	Consultee/ Commentator	Comments [sic]	Action
		HIV risk and PrEP eligibility involves the consideration of various factors. These factors are considered in the context of past, current, and potential future risk/behaviours. • Clinical indicators • Population-level indicators • Sexual behaviours/sexual network indicators • 'Other' risk indicators More recently, there has been a move away from 'eligibility criteria' in favour of a more person-centred, sexual behaviour and sexual networks approach. https://www.bhiva.org/PrEP-guidelines **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which cabotegravir injections will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;**	

Section	Consultee/ Commentator	Comments [sic]	Action
		• **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** **NICE intends to evaluate this technology through its Single Technology Appraisal process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).**	
	UK-CAB (joint response)	**Where do you consider cabotegravir injections will fit into the existing care pathway for pre-exposure prophylaxis of HIV-1?** Cabotegravir should be available where existing oral-based PrEP is prescribed e.g. sexual health services. However, it is known that current PrEP access is insufficient, and other healthcare and community settings would provide significant benefit to HIV prevention efforts by making PrEP available. We would urge an expedition of implementation trials and research to determine what other settings could effectively deliver PrEP – both as oral and injectable interventions. **Would cabotegravir injections be a candidate for managed access?** We believe there is enough real-world evidence to demonstrate that Cabotegravir Injectable works as PrEP. If there is any uncertainty of the cost effectiveness of the intervention then managed access should be explored.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		In what situations is cabotegravir expected to be used in clinical practice? For example, are cabotegravir injections expected to be used in place of oral PrEP? As outlined within our response to the subgroups, we do not see this as a replacement, but complementary option to provide PrEP to people in circumstances where an oral-based treatment may put them at harm, due to clinical issues with taking oral treatments, and other social/lifestyle factors. **Will cabotegravir injections need to be administered in healthcare settings?** At present yes. **How do patients and clinicians determine a person's level of risk for acquiring HIV-1?** Decisions should be person-centred and individualised, but reflect known understanding of HIV-risk, e.g. clinical indicators (such as frequent PEP use, or STI diagnoses); population factors (engaging in sexual networks with high-prevalence of HIV) etc.	
	ViiV Healthcare	Please see responses to the consultation questions below.	No action required.
Additional comments on the draft scope	BHIVA	None	No action required.
	CHIVA	None	No action required.
	Gilead	Gilead Sciences increasingly recognise that the current pharmacological and non-pharmacological HIV prevention and control strategies (such as effective treatments for people living with HIV, consistent and correct use of condoms, etc.) are insufficient to halt the transmission of HIV and as such may impact both global and the UK government's ambition of getting to zero HIV transmissions by 2030 as outlined in the HIV Action Plan. Therefore,	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		preventive options such as PrEP and equitable access to this are key for combatting HIV acquisition, especially in those vulnerable and high-risk populations in whom transmission rates either tend to plateau or continue to increase.	
	HIVPA	None	No action required.
	LGBT Foundation	N/A	No action required.
	NHIVNA	**Where do you consider cabotegravir injections will fit into the existing care pathway for pre-exposure prophylaxis of HIV-1?** Cabotegravir should be added as a first line regimen to the current HIV guidelines as part of the combination prevention methods, focusing on addressing the patient need, as they might be very different for each individual. **Would cabotegravir injections be a candidate for managed access?** Yes, it will be a very good way to secure evidence for the populations that are most in need of this intervention. **Do you consider that the use of cabotegravir injections can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes, there are a lot of underserved populations that could benefit from injectable PrEP: Women (of all ages for different reasons), young people, people who use drugs, people with mental health or physical problems whose adherence might be compromised, people with unstable housing or facing homelessness, people who travel to countries where carrying medication could prove problematic, people in abusive relationships, people on medication that interact with the oral regimens or	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		that are dealing with pill burden, who can't access PrEP, or adhere to oral tablets for any other reason, or require discretion for any other reason. **Have all relevant comparators for cabotegravir injections been included in the scope?** No (see above) **Are the outcomes listed appropriate?** Yes (see above) **Are there any subgroups of people in whom cabotegravir is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Yes (see above) **In what situations is cabotegravir expected to be used in clinical practice? For example, are cabotegravir injections expected to be used in place of oral PrEP?** Yes Cabotegravir injections should be considered for anyone at risk of acquiring HIV **Will cabotegravir injections need to be administered in healthcare settings?** Not necessarily. To ensure IM administration, a highly skilled and trained professional should be administering the injections. The administration, however, could take place in sexual health clinics, community settings like charity organisations and community pharmacies, or even at home. The monitoring could happen in collaboration with a sexual health clinic and/or hospital/GP service if the administration is taking place in the community setting.	

Section	Consultee/ Commentator	Comments [sic]	Action
		How do patients and clinicians determine a person's level of risk for acquiring HIV-1? Healthcare professionals use the BHIVA guidelines, chapter 5 : Recommend PrEP (i) : HIV-negative MSM and trans women who report condomless anal sex in the previous 6 months and on-going condomless anal sex. (1A) (ii) HIV-negative individuals having condomless sex with partners who are HIV positive, unless the partner has been on ART for at least 6 months and their plasma viral load is <200 copies/mL. (1A) Consider PrEP on a case-by-case basis PrEP may be offered on a case-by-case basis to HIV-negative individuals considered at increased risk of HIV acquisition through a combination of factors that may include the following: <u>Population-level indicators</u> • Heterosexual black African men and women • Recent migrants to the UK • Transgender women • People who inject drugs • People who report sex work or transactional sex <u>Clinical indicators</u> • Rectal bacterial STI in the previous year • Bacterial STI or HCV in the previous year • Post-exposure prophylaxis following sexual exposure (PEPSE) in the previous year; particularly where repeated courses have been used	

Section	Consultee/ Commentator	Comments [sic]	Action
		Sexual behaviour/sexual-network indicators • High-risk sexual behaviour: reporting condomless sex with partners of unknown HIV status, and particularly where this is condomless anal sex or with multiple partners • Condomless sex with partners from a population group or country with high HIV prevalence (see UNAID definitions [1]) • Condomless sex with sexual partners who may fit the criteria of 'high risk of HIV' detailed above • Engages in chemsex or group sex • Reports anticipated future high-risk sexual behaviour • Condomless vaginal sex should only considered high risk where other contextual factors or vulnerabilities are present Drug use • Sharing injecting equipment • Injecting in an unsafe setting • No access to needle and syringe programmes or opioid substitution therapy Sexual health autonomy Other factors that may affect sexual health autonomy • Inability to negotiate and/or use condoms (or employ other HIV prevention methods) with sexual partners • Coercive and/or violent power dynamics in relationships (e.g. intimate partner/domestic violence) • Precarious housing or homelessness, and/or other factors that may affect material circumstances	

Section	Consultee/ Commentator	Comments [sic]	Action
		• Risk of sexual exploitation and trafficking **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits** • BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2018 https://www.bhiva.org/file/5b729cd592060/2018-PrEP-Guidelines.pdf • CDC PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2021 UPDATE A CLINICAL PRACTICE GUIDELINE https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf • WHO Guidelines on long-acting injectable cabotegravir for HIV prevention https://www.who.int/publications/i/item/9789240054097 • Raphael J. Landovitz, M.D. et al, 2021, Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women, The New England Journal of Medicine, N Engl J Med 2021; 385:595-608 DOI: 10.1056/NEJMoa2101016 • Prof Sinead Delany-Moretlwe, PhD et al, 2022, Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial, The Lancet, VOLUME 399, ISSUE 10337, P1779-1789, MAY 07, 2022 • IAS 2023 EPC0361: Greshon Rota ET AL, Pharmacy provider perceptions of pharmacy-delivered injectable PrEP in Kenya • IAS 2023 LBPEE01: Rupa R. Patel et al, Feasibility of Long-Acting Injectable Cabotegravir PrEP Initiation and Administration by Community Health Workers and Early Aspects of the PrEP Injection Care Continuum in a Primary Care Center in Washington, D.C. • IAS 2023 LBEPX52: Juliane Etima et al, Willingness to use Long-Acting Injectable Cabotegravir (CAB-LA) or Oral TDF/FTC for Pre-	

Section	Consultee/ Commentator	Comments [sic]	Action
		Exposure Prophylaxis (PrEP) During Pregnancy in Africa: Findings from the HPTN-084 Qualitative Sub-study • IAS 2023 EPC0348: Haoyi Wang et al, Adherence is the key: Targeting long-acting injectable cabotegravir to MSM current oral PrEP users with low adherence would be highly effective and efficient, a modelling study with Dutch perspectives • IAS 2023 EPC0403: L. Magno et al, Awareness and intention to use event-driven and long-acting injectable pre-exposure prophylaxis among adolescent and young men who have sex with men and transgender women in Brazil • IAS 2023 EPC0375: Phan ThiThu Huong et al, Willingness to use and preference for long-acting injectable PrEP among men who have sex with men and transgender individuals in Vietnam	
	NHSE	None	No action required.
	Terrence Higgins Trust	None	No action required.
	UK-CAB (joint response)	None	No action required.
	ViiV Healthcare	NA **Where do you consider cabotegravir injections will fit into the existing care pathway for pre-exposure prophylaxis of HIV-1?**	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Cabotegravir will fit into the existing pathway to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals for whom oral PrEP is not appropriate. **Would cabotegravir injections be a candidate for managed access?** No, ViiV does not consider that cabotegravir is a candidate for a managed access scheme. **Do you consider that the use of cabotegravir injections can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Yes, ViiV considers there are some qualitative benefits that would not be captured in the QALY. These benefits include: • The addition of a new modality such as long-acting injectable PrEP for people at risk of HIV-1 acquisition in England and Wales will enable clinicians to offer an option to people for whom oral PrEP is not appropriate and in turn reduce the HIV transmission in England and Wales supporting the NHS's commitment to zero new transmissions of HIV by 2023[1]. • Potential unquantified benefits linked to regular contact with healthcare services[8]. • Effects on wellbeing that are not captured by generic preference-based utility measures such as the psychological impact of disclosure due to the stigma associated with PrEP or HIV and the burden of the reminder from daily use of PrEP[9-11]	

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all relevant comparators for cabotegravir injections been included in the scope? Answered above. **Are the outcomes listed appropriate?** Answered above **Are there any subgroups of people in whom cabotegravir is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Whilst ViiV has not defined specific subgroups, the superior efficacy of cabotegravir compared to oral TDF/FTC has been demonstrated in the clinical trials HTPN083 (in men who have sex with men and transgender women) and in HPTN084 (in cisgender women). In addition, cabotegravir as the first injectable long-acting agent for PrEP is expected to offer significant benefit and to be cost-effective in individuals at risk of HIV-1 for whom oral PrEP is not appropriate. Thus, this should be the target population for this appraisal. **In what situations is cabotegravir expected to be used in clinical practice? For example, are cabotegravir injections expected to be used in place of oral PrEP?** Cabotegravir is expected to be used in at-risk individuals for whom oral PrEP is not appropriate.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Will cabotegravir injections need to be administered in healthcare settings? Yes, as it should be administered by a healthcare professional. **How do patients and clinicians determine a person's level of risk for acquiring HIV-1?** A person's level of risk for acquiring HIV-1 is currently determined as per the BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2018[12]. PrEP may be offered on a case-by-case basis to HIV-negative individuals considered at increased risk of HIV acquisition through a combination of factors that may include the following: population-level indicators, sexual behaviour/sexual-network indicators, clinical indicators, sexual health autonomy etc [8] **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** The Phase IIb/III, multicentre, double-blind, randomised HIV Prevention Trials Network (HPTN) 083 study (N=4,566) demonstrated the superiority of cabotegravir compared with daily oral TDF/FTC in reducing the risk of HIV acquisition among cisgender men and transgender women (TGW) who have sex with men (13 vs 39 incident HIV infections were observed in the cabotegravir arm vs the daily oral TDF/FTC arm, translating into a 66% reduction in the risk of incident HIV infection in the cabotegravir arm relative to daily oral TDF/FTC arm (HR 0.34; 95% CI 0.18, 0.62; p-value<0.0001). The Phase III, multicentre, double-blind, randomised HPTN 084 study (N=3,224) demonstrated the superiority of cabotegravir compared with daily oral TDF/FTC in reducing the risk of HIV acquisition among cisgender women	

Section	Consultee/ Commentator	Comments [sic]	Action
		(3 vs 36 incident HIV infections, respectively), translating into an 88% reduction in the risk of incident infection relative to daily oral TDF/FTC (HR 0.12; 95% CI 0.05, 0.31; p-value<0.0001). **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the population for which cabotegravir injections will be licensed;** As cabotegravir will potentially be the first HIV PrEP appraisal to go through the NICE process, some important considerations are required as described below. Potential equality considerations relate to groups protected under the Equality Act 2010 on grounds of: **Gender Identity:** Transgender individuals are at risk for, and disproportionately affected by, HIV. Globally, trans women and trans feminine individuals are 66 times more likely to acquire and live with HIV, with trans men and trans masculine individuals 6.8 times more likely, compared to other individuals aged over 15 years [13]. In the Global North including Europe, transgender individuals are 48.4 times more likely to acquire and live with HIV. Individual level risk factors significantly increase the risk of HIV acquisition, including condomless sex, coinfections with other sexually transmitted infections, transactional sex, and shared use of needles for	

Section	Consultee/ Commentator	Comments [sic]	Action
		hormone and/or silicon injections. These individual risk factors intersect with and result from other factors such as mental health difficulties, substance use, and many forms of marginalisation and stigmatisation that limit, among other things, educational and work opportunities, as well as legal recognition of one's chosen gender. These intersectional risk factors result in a dynamic increased risk of acquiring HIV among transgender individuals. **Ethnicity:** People of Black African ethnicity and people coming to the UK from countries with a high HIV prevalence, are at risk for and disproportionately affected by HIV. In England in 2021, 25% of new diagnoses were in individuals previously diagnosed abroad[14] . People of Black African ethnicity constitute the second largest ethnic group (19%) of those first diagnosed with HIV in England. Among people exposed by heterosexual contact, diagnoses among those first diagnosed in England were highest among those of Black African ethnicity (37%). In England, people of Black African ethnicity are also at higher risk of living with undiagnosed HIV[15]. Among heterosexual people, there is a disproportionate impact of new HIV diagnoses on people of Black African ethnicity[1] with Black African women representing the second largest group of people living with HIV in England[16]. **Sexual Orientation:** Gay, bisexual and other men who have sex with men are at risk for and disproportionately affected by HIV. In England in 2021, men exposed through sex between men accounted for 36% of new HIV diagnoses first made in England, increasing by 3% compared to 2020, largely affected by increased diagnosis outside of London [2]. In England, gay, bisexual and other men who have sex with men represent the largest group of people living with undiagnosed HIV [3]. Despite a reduction in new HIV diagnoses in England between 2014 and 2019 [4], an increasing trend in late diagnosis is observed among gay, bisexual and other men who have sex with men, with 29% in 2019, to 30% in 2020, to 37% in 2021, whereby late	

Section	Consultee/ Commentator	Comments [sic]	Action
		diagnosis is associated with poor outcomes, increased risk of ongoing HIV transmission and high healthcare costs [17].Transgender individuals, women of Black African ethnicity, and gay, bisexual and other men who have sex with men, represent key populations at risk of HIV. These populations are also disproportionately affected by the wider social, economic, and environmental circumstances that impact on people's health, known as the social determinants of health, which influence health inequalities[17, 18]. Other important considerations are as follows: **Stigma and discrimination**: PrEP stigma is a barrier to PrEP interest, uptake, and continuation that manifests at multiple levels. PrEP use has been linked to a range of negative judgments and social concerns, including fear that others will misperceive PrEP use as HIV treatment and assume that the "PrEP user" is a person living with HIV (reflecting HIV stigma)[9]. HIV-related stigma is a commonly cited barrier to PrEP use, in a study of people of Black African heritage, 65% cited stigma as a major barrier to the uptake of PrEP. Women of black African ethnicity were wary of accessing sexual and reproductive health services due to fears of negative reactions from people in their communities[10].The reduction of PrEP stigma and its negative impact requires a shift in perspective, language (as described in 'other considerations'), and programmes. Such a shift is necessary to ensure effective uptake of PrEP as a prevention strategy and improve its utilisation by the individuals who need it most. Although PrEP stigma is often experienced at the community level (i.e., by potential and current users), it can be reinforced and even amplified by public health programs, policy, and research. PrEP stigma disproportionately impacts disadvantaged groups and impedes scalability by influencing behaviour of both patients and providers [11].	

Section	Consultee/ Commentator	Comments [sic]	Action
		This information further supports the importance of new PrEP options to prevent HIV-1 transmissions. • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** No Comment • **could have any adverse impact on people with a particular disability or disabilities.** No Comment	

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope