National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cabotegravir and rilpivirine for treating HIV-1 ID3766

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	HIV i-Base	This scope seems reasonable. Cabotegravir/rilpivirine LA (CAB/RPV-LA) is the first longacting HIV combination (dosing is being studied every one or two months - ie either 6 or 12 injections a year) and it is also the first full combination that can be given by injection (rather than oral pills). While there is a high level of general interest in non-oral combinations among a wide range of people living with HIV, such long-acting options have very important clinical advantages for specifics situations. This includes the option to overcome complex situations where, despite existing support, adherence to treatment is difficult. Two examples include psychological difficulties related to behavioural and neurocognitive problems that can affect people at all ages or age-specific times where adherence is well-documented as difficult like adolescence. Other examples should be highlighted as part of the scoping review. If CAB/RPV-LA is close to being price-neutral to current combinations, wide access should be easy to recommend. If priced considerably higher, then clinical criteria should ensure that people with clinical needs outlined above, are prioritised.	Comments noted. No action required.

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Wording	NHS England and Improvement (HIV CRG)	This needs to be more precisely defined. Naïve versus experienced, no resistance etc	Comment noted. After discussion at the scoping workshop, the remit was changed to specify adults who are virologically suppressed.
	ViiV Healthcare	ViiV Healthcare proposes amending the draft remit wording to align with the anticipated marketing authorisation as follows: To appraise the clinical and cost-effectiveness of long-acting cabotegravir injection (CAB LA) in combination with long-acting rilpivirine injection (RPV LA) for the treatment of HIV-1 infection in adults who are virologically suppressed.	Comments noted. After discussion at the scoping workshop, the remit was changed to specify long-acting injections and to specify adults who are virologically suppressed.
Timing Issues	NHS England and Improvement (HIV CRG)	moderate	Comment noted.
	National HIV Nurses Association (NHIVNA)	Urgent for those who cannot or will not take oral medication, desirable for others.	Comment noted.
	Gilead	Non-urgent: There are other alternative treatments with high efficacy, safety and tolerability widely available.	Comment noted.
	HIV i-Base	Important, such that expanded access/named-patient access should be available until approval.	Comment noted.

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	ViiV Healthcare	This appraisal should be considered with urgency. While many HIV positive people are virally suppressed on oral medication this does not represent optimisation of their care given that: some patients have sub-optimal adherence; others have psychological issues reinforced by daily pill taking; and others have medical conditions making oral treatment challenging. CAB LA and RPV LA offers a new treatment approach for these people.	Comment noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	National HIV Nurses Association (NHIVNA)	Seems pretty accurate and not over-complicated.	Comment noted. No action required.
	ViiV Healthcare	ViiV Healthcare suggests the following amends are made for improved accuracy and completeness: First paragraph Suggested wording amendment - “The destruction of these cells leaves people living with HIV unable to fight off infections and some other diseases” amended to “The destruction of these cells leaves people living with HIV with a suppressed immune system and vulnerable to infections and some other diseases”. Second paragraph	Comments noted. Suggested wording has been adopted for the first paragraph. The background information has been updated to include brief discussion of reasons for treatment switching that are not because of virologic failure. The background section of the scope aims to provide a brief summary of the condition and how it is managed, it is not designed

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		Of the 97% of patients deemed virologically supressed it is important to note that this population is still dynamic; an estimated 10% of these patients switch (elements of) antiretroviral therapies (ART) due to virological failure and for non-virologic failure reasons (i.e. whilst virologically suppressed) (BHIVA 2016). People that require a treatment switch due to non-virologic failure are the population under consideration for this proposed appraisal. This should be reflected in the Background Information. Third paragraph For completeness of information, the Background Information section should highlight that whilst ARTs are efficacious, tolerability and toxicity concerns are recognised across all classes of ART and chronic exposure to drug regimens can lead to both short- and long-term toxicities. This illustrates the importance of having alternative treatment options available. The Background Information does not reflect the value in optimising treatment to maintain virologic response, improve adherence and prevent onward transmission. The background information also needs to provide the critical patient perspective that separates living with HIV-1 from other chronic diseases specifically the associated stigma and psychological impact of HIV infection on individuals (BHIVA 2016; PHE 2017; Murungi 2017). Suggested wording amendment - “ARTs are often used in combination to avoid the disease adapting and becoming resistant” should be amended to “ARTs are usually used in combination to avoid the virus adapting and becoming resistant.”	to be exhaustive in its detail. Where relevant, the additional benefit of alternative treatment options and value of optimising treatment will be considered during the appraisal. The suggested wording amendment has been adopted. Thank you for your comments.

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Background information	HIV i-Base	This text is not particularly helpful or well-written and although slightly more proofed than those for ibalizumab and fostemsavir it broadly has the same problems. It is not helpful to mix treatment and prevention. I have never seen ART referred to in the plural. Choice of ART is not really complex for most people (has NICE looked at the guidelines). The reference to 95% adherence is from a 1998 study and unlikely to be accurate based on current FDCs. Is this really the best NICE can do? Doesn't pass readability criteria for public info: https://www.readabilityformulas.com/free-readability-formula-tests.php Readability Consensus Based on (7) readability formulas, we have scored your text: Grade Level: 12 Reading Level: difficult to read. Reader's Age: 17-18 yrs. old (Twelfth graders)	Response noted. No action required.
	MSD	It would be useful for this section to outline the general properties and rationale of long-acting antiretroviral therapy (ART), as well as the unmet needs that can potentially be addressed by this new treatment paradigm.	Comment noted. The background information has been updated to include brief discussion of reasons for treatment switching that are not because of virologic failure.
The technology/ intervention	National HIV Nurses Association (NHIVNA)	This is an IM injection that needs to administered every 2 months by a HCP (likely to be a nurse after the initial dose). It is not, unlike oral ART, self-administered by a patient.	Comment noted. The effect of implementing the technology on healthcare resource will be considered during the appraisal.

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	HIV i-Base	The document refers to twomonthly injections but many of the studies used monthly dosing. EU regulatory application refers to monthly injections. https://viivhealthcare.com/engb/media/pressreleases/2019/july/viiv-healthcaresubmits-regulatory-application-toeuropean-medic/	Comment noted. The description of the technology has been updated to include monthly injections as noted in the expected marketing authorisation.
	Gilead	Yes. However, to note: The draft scope states CAB/RPV has been studied in clinical trials compared with standard integrase inhibitor-based single tablet regimens. This is correct, but to clarify in the ATLAS trial – CAB/RPV was compared with anti-retroviral regimens comprising 2 NRTIs plus an INI, NNRTI, or a PI (as STRs or MTRs)	Comment noted. The description of the technology has been updated to note the various ART regimens CAB/RPV has been compared with.
	ViiV Healthcare	ViiV Healthcare proposes the following additions for accuracy and completeness: The Technology First paragraph Note the brand name for CAB LA is Vocabria. Note that the brand name Edurant refers to the oral formulation of rilpivirine. Suggested word amendment: “Rilpivirine (Edurant, Janssen) is a diarylpyrimidine non-nucleoside reverse-transcriptase inhibitor (NNRTI) of HIV-1” amended to “Rilpivirine is a diarylpyrimidine non-nucleoside reverse-transcriptase inhibitor	Comments noted. The description of the technology has been updated to note the various ART regimens CAB/RPV has been compared with and the brand names for cabotegravir and rilpivirine.

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		(NNRTI) of HIV-1 and currently only available as an oral formulation (Edurant, Janssen)." The brand name for RPV LA is Rekambys. Second paragraph "Cabotegravir and rilpivirine does not currently have a marketing authorisation for treating HIV-1, it has been studied in clinical trials compared with standard integrase inhibitor-based single tablet regimens" amended to "Long-acting cabotegravir and long-acting rilpivirine do not currently have a marketing authorisation for treating HIV-1; this regimen has been studied in clinical trials compared with a variety of ART regimens." Note that it is incorrect to state that the clinical trials have compared CAB LA and RPV LA with standard integrase inhibiter-based single tablet regimens; a broad range of regimens from across all available classes were included. Intervention No further comment.	
Population	NHS England and	No, see above	Comment noted. The population has been updated to specify 'Adults with HIV-1

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	Improvement (HIV CRG)		infection who are virologically suppressed on a stable regimen', therefore these would be treatment-experienced.
	National HIV Nurses Association (NHIVNA)	Do we need to differentiate between stable and complex patients here? What is the criteria for receiving injectable medications? All people with HIV-1 will require some form of ART but it would be practically impossible, due to service capacity, to treat all people with HIV-1 with injectable medications. How will clinicians decide on which sub-populations and/or individual patients will be eligible for this treatment? What about patients with resistance mutations on their strain of HIV? What about very treatment experienced patients? Could this be given in the home by community HIV nurses	Comments noted. These questions about implementation, subgroups, service capacity, resistance mutations and treatment experience will be explored during the appraisal. NICE will appraise this technology within its marketing authorisation for adults with HIV-1 infection who are virologically suppressed on a stable regimen.
	ViiV Healthcare	No, the population needs to accurately reflect the proposed indication as follows: Adults with HIV-1 infection who are virologically suppressed (HIV-1 RNA <50 copies /mL) on a stable regimen. Please also refer to the regulatory section for full details of the anticipated indication.	Comment noted. The population has been updated to reflect the proposed indication.
	Gilead	No	Comment noted. The population has been updated

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		• Not all people with HIV-1 would be eligible for this treatment. In the Phase 3 clinical trials, subjects were required to be virally suppressed for six months or greater, on first or second regimen, with no prior failure. Not all PLWHIV are suitable for, or would want IM injections	to reflect the proposed indication.
Comparators	NHS England and Improvement (HIV CRG)	Optimised background is not the correct comparator for this CBT/RPV will be used in first and second line so needs to be compared against INI containing regimens in patients without resistance. Also possibly DTG/RPV as oral therapy.	Comments noted. The comparator section has been updated to reflect discussion at the scoping workshop that suggested the appropriate comparator is 'Current antiretroviral treatment (established clinical management such as an integrase inhibitor-based regimen)'
	National HIV Nurses Association (NHIVNA)	Also compare with not being on ART? Injectables might be an option for patients who have refused daily oral medications or who lead chaotic lifes/poor service attendance.	Comment noted. NICE will appraise this technology within its marketing authorisation for adults with HIV-1 infection who are virologically suppressed on a stable regimen. Where relevant, any additional benefit of service redesign or increasing the population that would benefit from treatment will be considered during the appraisal.

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	HIV i-Base	This should be “current” ART rather than “optimised” ART (which doesn’t really make sense). Optimised has been copied perhaps form the ibalizumab and fostemsavir documents where it does make sense.	Comment noted. The comparator section has been updated to reflect discussion at the scoping workshop that suggested the appropriate comparator is ‘antiretroviral treatment (established clinical management such as an integrase inhibitor-based regimen)’.
	MSD	Please could clarity be provided on the meaning of “optimised ART” in this context? In order to maintain a broader perspective accounting for all currently relevant treatment options, MSD recommends that this section should be altered to “Established anti-retroviral therapy that represents up-to-date clinical practice”.	Comment noted. The comparator section has been updated to reflect discussion at the scoping workshop that suggested the appropriate comparator is ‘antiretroviral treatment (established clinical management such as an integrase inhibitor-based regimen)’.
	ViiV Healthcare	ViiV Healthcare suggests the removal of ‘Optimised’ to align with common terminology. We agree the comparator is established clinical ART management. Please see later response which seeks to refine the relevant comparators further.	Comment noted. The comparator section has been updated to reflect discussion at the scoping workshop that suggested the appropriate comparator is ‘antiretroviral treatment (established clinical management such as an

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			integrase inhibitor-based regimen)'.
Outcomes	MSD	MSD suggests that the wording for the change in HIV-1 RNA outcome be amended to the following for greater accuracy: "change in HIV-1 RNA count from baseline". MSD also considers that "treatment-emergent resistance" should be included in the list of outcomes.	Comments noted. After discussion at the scoping workshop, it was agreed that maintenance of viral suppression was the most important outcome of interest for this population. Treatment-emergent resistance has been included as an outcome.
	National HIV Nurses Association (NHIVNA)	All of the outcomes listed are valuable but a particular focus needs to be on adherence to treatment regimen and how, as HCPs, we assist patients in optimising this outcome. For example, what happens if patients miss an injection and how are patients recalled if they miss an injection? What are the parameters for early or late injections (for example if someone is away on holiday or with work can they have it a week early or late	Comments noted. The adherence to treatment regimen outcome has been kept in the scope to address these issues where possible. Where relevant, other issues concerning adherence will be considered during the appraisal.
	NHS England and Improvement (HIV CRG)	Need to consider the potential benefits in harms in more vulnerable groups likely to be prescribed this combination but who will not have in general been included in clinical studies	Comment noted. Where relevant, generalisability of the clinical studies will be considered during the appraisal.
	ViiV Healthcare	**Change in Viral Load**	Comments noted. Maintenance of virological

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		Note that change in viral load is less informative in studies assessing therapies aimed at a virologically suppressed population, although it will still be presented. The aim in these study populations is to maintain virological suppression. **Patients with Viral Suppression** In a virologically suppressed population who switch treatment, the outcome *"patients with viral suppression (undetectable viral load)*" should be amended to "*maintenance of virological suppression*". This amendment reflects how the outcome is measured in a virologically suppressed population. Three additional outcomes will be important to capture: • Preference and satisfaction for the long-acting treatment regimen • AIDS-defining events • Virologic rebound	suppression has been included as an outcome in the scope. After discussion at the scoping workshop, it was considered that AIDS-defining events should also be included, virologic rebound is the same concept as maintenance of virological suppression and preference and satisfaction for long-acting treatment regimen should be considered through the health-related quality of life measurement.
Economic analysis	Gilead	A lifetime horizon is preferred in chronic conditions in general, but assumptions may need to be made which may be challenging given the current environment (i.e. covid, limited/precious workforce and resources etc). Assessment of the impact of this treatment on the care pathway and patient time due to increased use of resources should be undertaken	Comments noted. No action required.
	MSD	Many pertinent patient-reported outcomes and experiences will be collected using instruments other than EQ-5D-3L, so the nuances of	Comments noted. Where relevant, the benefits and

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		some results may be lost in the process of converting data derived from HIV-specific questionnaires to EQ-5D. MSD suggests that a flexible and pragmatic approach should be adopted for assessing qualitative elements of treatment, taking into account the important contribution of efficacious and patient-preferred treatments towards people living well with HIV, the “4th 90” pillar of the UNAIDS 90-90-90 strategy.	limitations of using generic and disease-specific health-related quality of life data will be considered during the appraisal.
	National HIV Nurses Association (NHIVNA)	This has to include the clinical resources needed to administer the injectable which are likely to be above those used in the current standard of care? It will include more visits per year than current practice (6 visits whereas now only 1-2) and these visits will likely be with a nurse (HIV or otherwise) who will need to administer the injection. Is there capacity (workforce and space) in the existing HIV nursing teams to do this and which nurses will be expected to take on this responsibility? It is not economically viable to have band 7/8 nurse practitioners give IM injections every 2 months when they have advanced skills that could be used to undertake more complex tasks. If more money is put in to increasing the junior nursing workforce (to undertake the role of administering injectables) then what is the increased benefit of doing this over and above the current standard of care? Injectables might increase QALYs in patients who will not take oral medications and it may aid in supressing VL, increasing CD4 and subsequently assist in reducing disability and illness. Some patients report adverse effects to their mental health because they have to take a daily dose of medication. There is a possibility that injectables may reduce these adverse effects on mental health but this needs to be weighed up with the same feelings that people might have about attending an outpatient appointment in an HIV clinic (which would change to every 2 months, from every 6 months).	Comments noted. Where relevant, the effect of implementing the technology on healthcare resource will be considered during the appraisal. The health-related quality of life of patients will be considered during the appraisal. Thank you for your comments.

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		There maybe scope for this to be given at home by HIV community nurses and as this develops it maybe rededesigned for self-administration which would be beneficial	
	ViiV Healthcare	The economic analysis should include the key benefit of switching to a long-acting regimen, CAB LA + RPV LA. As such, adherence and onward transmission should be considered as part of the analysis.	Comments noted. No action required.
	HIV i-Base	If CAB/RPV-LA is close to being price-neutral to current combinations, wide access should be easy to recommend. If priced considerably higher, then clinical criteria should ensure that people with clinical needs outlined above, are prioritised.	Comments noted. No action required.
Equality and Diversity	NHS England and Improvement (HIV CRG)	See comments re children and young persons' access	The marketing authorisation for this technology specifies that it is for adults.
	National HIV Nurses Association (NHIVNA)	Particular focus needs to be on access to the technology for marginalised, vulnerable and disabled patients. Injectables offer the potential to treat HIV in people who, for various different reasons, might not take oral medications. These reasons are often linked to vulnerabilities such as reduced mobility and poor mental health which limit the ways in which people can access NHS services. If planned and delivered carefully they have the potential to offer a different treatment option to these groups of people.	Comments noted. The committee will consider how the recommendation requires consideration of equalities issues during the appraisal.
	MSD	Considering some of the existing barriers that impact upon ART access and use in Black women and other underserved populations, it would be useful for NICE to consider how best their final recommendations could	Comments noted. The committee will consider how the recommendation requires

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		be presented in a manner that supports equitable access for all populations.	consideration of equalities issues during the appraisal.
	Gilead	There could be potential limitations for those unable to travel to hospital for drug administration which could have an impact on access to this potential treatment.	Comments noted. The committee will consider how the recommendation requires consideration of equalities issues during the appraisal.
	HIV i-Base	Doesn't pass readability criteria for public info:	Comment noted. NICE aims to avoid unnecessary technical language when possible. However, as the scope is a technical document which will form the basis for an appraisal, it may be necessary to include technical language, particularly where there are no simple alternatives. In these cases, we aim to provide as much information as possible to make it understandable to the reader.
	ViiV Healthcare	ViiV Healthcare does not believe that the proposed remit and scope will need to change. As CAB LA + RPV LA will potentially be the first HIV appraisal through the NICE process, the following information may be of interest to note:	Financial insecurity is not an inequality issue. This element is not part of the protected characteristics. In regards to race and sexual orientation, the committee will need to

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		Potential equality considerations relate to groups protected under the Equality Act 2010 on grounds of: • Race: HIV infection disproportionately affects people of black African origin and people coming to the UK from countries with a high HIV prevalence. For example, the estimated prevalence of HIV among heterosexual women and men aged 15 to 74 years in England in 2018 was 36.6 per 1,000 (CrI 36.0 to 37.3) among black African people compared with 1.10 per 1,000 (CrI 1.08 to 1.15) among this population as a whole (PHE 2018). • Sexual Orientation: HIV disproportionately affects gay and bisexual men (GBM), who accounted for approximately 45,200 of the 94,900 people living with HIV (PLHIV) in England in 2018, an overall prevalence of 88 per 1,000 (CrI 77 to 102) among GBM in England aged 15 to 74 years (PHE 2018). Other important considerations are as follows: • Financial insecurity: An estimated 46% of women and 32% of men with HIV live at or below the poverty line (less than £20,000 per household) and 53% of people do not always have enough money to meet their basic needs (for example utilities, food, rent). An estimated 8% live rent free in accommodation provided by friends or family or some other form of temporary accommodation including shared housing where people can fear disclosure (PHE 2017). • Stigma and discrimination: 13% of people have not shared their HIV status outside of the healthcare setting. Sixteen percent of people with HIV are worried about being treated differently to others due to their HIV status, and an estimated 10% avoided seeking healthcare when they needed it because of their HIV (PHE 2017). Tackling stigma and discrimination (among other issues) will form part of the updated sexual	consider whether there are any issues to consider throughout guidance development.

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		and reproductive health strategy which the government committed to in October 2019 (Gov.UK 2019). This information further supports the importance of treatment options for people living with HIV-1.	
Other considerations	NHS England and Improvement (HIV CRG)	Feasibility for health services to deliver frequent injectable therapy to large numbers? Opportunities for self or non HCW administered therapy	Comments noted. Where relevant, the effect of implementing the technology on healthcare resource will be considered during the appraisal..
	Gilead	• IM administration every 2 months will have a significant impact on healthcare resource utilisation • Social-economic impact for the patient (time spent going to hospital, cost of going to hospital, etc.)	Comments noted. Where relevant, the effect of implementing the technology on healthcare resource will be considered during the appraisal.
	ViiV Healthcare	Consideration needs to be given to the previous way in which the new ARTs were made available to the NHS and people living with HIV-1 through the NHS England Specialised Commissioning route. These ARTs will form the comparator group for CAB LA + RPV LA. Recent products such as Juluca and Biktarvy were assessed through the NICE Commissioning Support Programme which is somewhat devolved from the NICE Reference case. The evidence submitted through the	Comments noted. Where appropriate, understanding of current commissioning policies will be considered during the appraisal.

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		commissioning support programme included only the pivotal study programme, estimated budget impact and service implementation. Other ARTs were assessed through NHS England Specialised Commissioning Clinical Priorities Advisory Group (CPAG) where decisions are based on the clinical data and acquisition cost. The absence of a NICE-appraised standard of care adds an additional level of complexity in this appraisal, which should be considered during the appraisal process. Given the changes to the appraisal process for HIV medicines in England, it may be informative under these circumstances to review previous HIV-1 assessments undertaken to date in Wales and Scotland.	
Innovation	National Aids Trust	Long-acting injectable treatment are a welcome addition to the range of treatment options available for people living with HIV. Research presented at the 2020 Conference on Retroviruses and Opportunistic Infections (Overton et al, Cabotegravir + Rilpivirine Every 2 Months Is Noninferior To Monthly: Atlas-2m Study) has shown that there is a preference for long-acting injectables among people living with HIV. People living with HIV can have difficulties with managing medications and adherence for a variety of reasons, including having difficulty swallowing, privacy concerns, or problems with an excessive pill burden. Long acting injectables can assist with adherence in these scenarios.	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	National HIV Nurses	The technology is innovative in so much as it offers the first real alternative to daily medications. Does this improve the way in which	Comment noted. Where relevant and appropriate, the

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	Association (NHIVNA)	current need is met? This is very specific to individuals. Some may argue ‘ yes I don’t have to remember to take a pill every day and/or I can’t take oral medications’ while others may feel ‘I don’t want to attend a clinic every 2 months, I don’t like injections, I have no side effects to my pill.’ It is a step-change in the current management of HIV as it offers this alternative but for some patients this alternative might be less desirable that the care they currently receive.	extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	NHS England and Improvement (HIV CRG)	High innovation Yes possibility of hidden benefits; better treatment coverage for those unable or unwilling to attend services frequently or take oral treatments. Could contribute to a residue of individuals in community with detectable viral loads assisting strategies to achieve zero deaths, zero transmission	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	UK Community Advisory Board	Long-acting injectable treatment presents new opportunities to improve the health and well-being of PLWH.	Comment noted. Where relevant and appropriate, the extent to which the

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		We know that many people still experience HIV-related stigma: one in eight have not shared their status with anyone outside their medical team (Positive Voices, PHE). We know from our own recent research looking at the impact of the current COVID-19 pandemic that many people living with HIV are already worried about their medication being found by those who are not aware, something an injectable treatment could alleviate. The UK has already successfully met the UNAIDS 90-90-90 targets. However, there are populations and groups of people within the overall HIV population who are yet to achieve these results. Of particular concern are young adolescents. We know that only 89% of 15-2 year olds on ART were virally supressed in 2018, compared to 97% of the overall HIV population (PHE, 2019). Young people are one group that could benefit from an intervention that isn't tablet based, where there is no need to hide tablets, and potential to address the "fatigue" of daily pills which some young people face when they have been taking treatment since birth. Other groups that could benefit include the small numbers of people who struggle with dysphagia, removing the barrier of needing to swallow daily pills and improving their well-being.	technology may be innovative will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	Gilead	• Long acting injectables may reduce HIV related stigma experienced by PLWH, as no daily reminder of HIV positivity when taking daily oral medications. • Some individuals may feel LAI is more convenient than taking daily oral medication.	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide

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			evidence on the innovative nature of its product in its submission. No action required.
	MSD	The advent of long-acting therapy represents a step-change in terms of how ART is administered and the resultant impact on service provision. Delivery of long-acting therapy via this method presents an important opportunity, but it will be important to consider the needs, preferences and suitability of differing patient populations for respective therapy options.	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	HIV i-Base	Definitely yes, especially if approved by EMA (assuming EU regulation is still recognised).	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative

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			nature of its product in its submission. No action required.
	ViiV Healthcare	Life-long daily ART remains a significant challenge for people living with HIV-1, even with modern simplified treatment regimens. CAB LA + RPV LA will be the first long-acting HIV treatment regimen for maintenance of virological suppression that does not require ongoing daily, oral administration. CAB LA + RPV LA is administered every 2 months, so that there is no longer an ongoing daily requirement to remember to take medication. The individual remains virally suppressed without the need for further action until the next injection visit, and with no possibility of suboptimal adherence. CAB LA + RPV LA represents a step-change in the treatment of HIV for those individuals who find life-long oral administration of ART challenging to adhere to. This includes people at risk of sub-optimal adherence (such as through changes in life style or presenting with signs of daily pill fatigue), the psychological impact experienced by some individuals (living with the fear of disclosure or the reminded stigma of having HIV that taking tablets daily brings) as well as ongoing medical conditions (such as GI-associated issues). In each of these cases it is challenging to demonstrate the true benefit of a long-acting regimen within the confines of a traditional HTA framework. These benefits are not captured as part of the standard non-inferiority evidence base to prove the maintenance of virological suppression. Understanding the potential benefit of a long- acting regimen to the individual is critical to the appraisal. We plan to capture these patient benefits using evidence outside of the clinical study programme and present as an estimated QALY benefit to demonstrate what this gain could look like. We believe this will likely underestimate the overall benefit that CAB LA + RPV LA will offer.	Comment noted. Where relevant and appropriate, the extent to which the technology may be innovative will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.

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Questions for consultation	ViiV Healthcare	**Have all relevant comparators for cabotegravir and rilpivirine been included in the scope?** Yes, the term 'established clinical ART management' is factually correct (see previous comment requesting removal of 'optimised'). With focus on the proposed Decision Problem for this appraisal, the most relevant comparator ARTs are those that virologically suppressed people are switching to (due to non-virologic reasons) i.e. in an attempt to further optimise their care beyond viral suppression. Early physician insights and market dynamics data suggest that the relevant comparators are as follows: • Emtricitabine/tenofovir alafenamide + Dolutegravir (FTC/TAF+DTG) (brand name: Descovy+ Tivicay) • Emtricitabine/tenofovir alafenamide + Raltegravir (FTC/TAF+RAL) (brand name: Descovy + Isentress) • Emtricitabine/tenofovir alafenamide + Darunavir/cobicistat (FTC/TAF+DRV/c) (brand name: Descovy + Rezolsta) • Bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) (brand name: Biktarvy) • Doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) (brand name: Delstrigo) • Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/c/FTC/TAF) (brand name: Symtuza) • Emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF) (brand name: Odefsey) • Abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) (brand name: Triumeq) **How should established clinical management be defined?** Established clinical management should be defined based on the following documents: • BHIVA Guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy (BHIVA 2016).	Comments noted. No action required.

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		• BHIVA treatment guidelines: 2019 interim statement on two-drug regimens (an extension to the 2016 Guidelines) (BHIVA 2019)
		• EACS (2019) European AIDS Clinical Society Guidelines (EACS 2019)
		• Best Practice in HIV Prescribing (NHS England 2019)
		• The following Specialised Commissioning policies (NHS England):
		  ○ Dolutegravir / lamivudine for the treatment of HIV-1 infected adults and adolescents over 12 years of age
		  ○ Dolutegravir-rilpivirine for treating HIV-1 in adults
		  ○ Elvitegravir/cobicistat/emtricitabine/tenofovir for treatment of HIV in adults
		  ○ Dolutegravir for treatment of HIV-1 infection (all ages)
		  ○ Doravirine for the treatment of HIV-1 in adults
		  ○ Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents
		  ○ Bictegravir-emtricitabine-tenofovir alafenamide for the treatment of HIV-1 in adults
		
		As per the Background Information section, selection of an appropriate ART regimen is individualised for the person with HIV-1 based on a broad range of factors, both clinical and non-clinical.
		
		What number of patients are expected to be eligible for treatment with cabotegravir and rilpivirine?
		Based on the figures and commentary provided on the Background Information section, of the estimated 10% of people who are virologically suppressed and in need of a change to their ART regimen (an estimated 9,000), the uptake of CAB LA + RPV LA is expected to be a small proportion of this switching population. This is owing to a number of factors a) CAB LA + RPV LA will be licensed for adults, virologically suppressed requiring a switch due to non-virologic failure reasons b) usage would be reserved in line with regional treatment algorithms c) a switch to a newer ART is subject to a multi-disciplinary team decision which as such acts to gatekeep usage for those people most likely to benefit.	

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		Are there any subgroups of people in whom cabotegravir and rilpivirine is expected to be more clinically effective and cost effective or other groups that should be examined separately? It is not expected that there will be clinically defined sub-groups of people in whom CAB LA + RPV LA will be more clinically effective and cost-effective. ViiV Healthcare do expect there will be certain virologically supressed people in need of a treatment switch who would benefit from a long-acting regimen as an alternative to oral therapy. **In what situations is cabotegravir and rilpivirine expected to be used in clinical practice? For example, are cabotegravir and rilpivirine expected to be used in place of single tablet regimens or are they expected to be an alternative to other regimens as well?** The pivotal study evidence and the anticipated licensed indication support the use of CAB LA in combination with RPV LA for adults who are virologically suppressed and on a stable regimen [redacted] The decision to switch people to CAB LA and RPV LA will be limited to those people most likely to benefit from a long-acting treatment and who are able to adhere to the regimen (the service for administration). Key examples for a decision to switch to a long-acting non-oral regimen include: • To support an individual's adherence to a treatment regimen ○ The physician may consider the individual to be at risk of sub-optimal adherence to daily oral therapy, following a physician-patient discussion at a follow-up appointment. This could be as a result of, for example, lifestyle changes or signs of daily pill fatigue. The physician would counsel people starting oral regimens regarding the importance of not missing daily doses in order to avoid the risk of resistance developing. A patient who was virologically suppressed on their initial treatment regimen may feel that they cannot be confident they will be able to keep up this level of adherence and be fearful about the	

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		consequences for themselves and also their partners (as they need to maintain undetectability in order to prevent onward transmission).
		• To support an individual's anxiety associated with living with HIV-1 infection and their ability to live their life.
		  ○ For example, living with the fear of disclosure; the stigma personally felt by the individual, being reminded daily, of their HIV infection by their oral regimen. For some, it's the anxiety of forgetting a dose.
		• To support an individual's medical condition(s)
		  ○ For example, GI-related issues such as, malabsorption, problems with swallowing tablets, oesophageal strictures.
		
		The examples provided are based on physician insights and also reflect those people transitioned to CAB LA and RPV LA as part of an ongoing compassionate use programme for individuals who have no available treatment alternatives and/or limited treatment options (e.g., who are unable to participate in the Phase III clinical studies or do not qualify), and, as a result of an underlying medical condition, are in need of parenterally administered drugs to construct an effective antiviral regimen.
		
		Therefore, CAB LA + RPV LA would offer an alternative to oral therapy for virologically suppressed people, where the oral route of administration itself poses a risk of sub-optimal treatment management.
		
		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.
		Adoption is anticipated to fall in line with the current service specification and regional variation is expected.	

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	Gilead	Consideration should be given to service reconfiguration that will happen due to COVID-19 and how that will affect the continued need to reduce health care utilisation and patient contact/time spent in hospital if new services need to be implemented	Comments noted. No action required.
Additional comments on the draft scope	HIV i-Base	Access to new treatments in the UK should be guided by passing the stringent criteria used by the EMA for EU approval. It is difficult to support extended delays after approval for UK citizens to be able to access these drugs.	Comments noted. No action required.
	NHS England and Improvement (HIV CRG)	Need a lot more detail	Comments noted. Following the scoping workshop, appropriate additional detail has been added throughout the scope.
	National HIV Nurses Association (NHIVNA)	Injectable HIV medication are advantageous for a small number of patients who have particular needs that, in part, cannot be met by offering oral HIV medications. Clinical resources are a big issue particularly with regards to the nursing workforce and as it stands it wouldn't be practically possible to offer injectable HIV medications to a large number of patients. We have 4500 patients in our cohort and I would estimate that we could currently manage around 30-50 people on injectables. A patient may be prescribed injectable medications by an HIV consultant and asked to be seen again in 6 months' time but there is a considerable amount of work that potentially needs to go in to that patients' care before they are seen again. This involves administering the medication, chasing DNA's and managing adverse events (including injection site issues) which would be in the remit of the nurse. Many HIV nurses are already managing caseloads of complex patients, dealing with psycho-social issues and often managing services so unless there is an increased investment in the nursing workforce within HIV services	Comments noted. Where relevant, the effect of implementing the technology on healthcare resource will be considered during the appraisal.

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		then injectable HIV medications can only be offered to a small number of patients. We need to be very clear who can have this treatment and don't underestimate peer discussions and pester power if this is a desirable way to take HIV treatment we may well be inundated with requests. We need to look at how this will be delivered and by who as this will add to nurse workload	
	ViiV Healthcare	**Section: Related NICE recommendations and NICE Pathways** Reference to ibalizumab and fostemsavir should be removed as these technologies address a heavily treatment experienced population with multidrug resistant HIV-1 infection, who are unable to construct a stable ART regimen and for this reason, they are not relevant to the proposed appraisal of CAB LA + RPV LA. As CAB LA + RPV LA will not be licensed for use in a treatment naïve population, we also suggest the removal of: • NICE Guideline 60 (2016) HIV testing: increasing uptake among people who may have undiagnosed HIV • NICE quality standard 157 (2017). HIV testing: encouraging uptake • NICE pathway (2019) HIV testing and prevention **Section: Related National Policy** Relevant National policies and Guidelines include: BHIVA (2016) BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update) BHIVA (2019) BHIVA treatment guidelines: 2019 interim statement on two-drug regimens EACS (2019) European AIDS Clinical Society Guidelines	Comments noted. Related recommendations and pathways include all NICE guidance on the condition to show previous aspects of the disease covered by NICE guidance. Related national policy has been updated to include the suggested guidelines, thank you for your comments.

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		Historical HTA assessment of treatments for HIV-1 undertaken by the AWMSG and SMC. Please also refer to previous comment for inclusion of NHS E Specialised Commissioning policies	

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

Janssen
AbbVie