Discussion Paper

Research Priorities on Implementing Cabotegravir for PrEP in Australia

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Table of Contents

Executive Summary

To prepare for the introduction of long-acting injectable Cabotegravir (CAB-LA) as HIV pre-exposure prophylaxis (PrEP) in Australia, researchers from the Kirby Institute at UNSW Sydney and Alfred Health in Melbourne were funded by ViiV Healthcare and NSW Health to conduct a range of activities to determine research priorities, consult with stakeholders in the Australian HIV sector, and develop a protocol and funding application for an implementation-focused clinical trial.

CAB-LA involves an intramuscular injection every eight weeks, and its efficacy as PrEP has been proven in two randomised clinical trials internationally. Despite its high efficacy, potential issues with CAB-LA as PrEP include: how to optimise the delivery of 8-weekly injections; the pharmacokinetic "tail" whereby CAB-LA is in the body at low levels for up to 12 months after the last injection leading to a potential for drug resistance if the person were to acquire HIV; a small number of "breakthrough" HIV infections observed in GBM despite on-time injections; delayed detection of HIV in those who acquire HIV while taking CAB-LA; and limited data on time to protection after commencing CAB-LA injections.

We conducted:

1) A scoping literature review of 121 published articles on CAB-LA;
2) A survey on values and preferences about PrEP among 1608 Australian gay and bisexual men (GBM);
3) Qualitative interviews with 27 HIV sector stakeholders and clinical service providers; and
4) Co-design workshops with PrEP users and potential users, and separately with clinical service providers.

Together, these formative research activities found high interest in and preference for long-acting PrEP generally and CAB-LA specifically among GBM, and support for the idea of introducing CAB-LA into Australia among service providers and stakeholders as an additional PrEP choice. However, there was some hesitancy and ambivalence from some stakeholders, service providers and PrEP end-users about the specifics of introducing CAB-LA into practice, given the additional burden on clinics that may come with six visits a year. Our participants were able to articulate populations that may be most suitable for CAB-LA. They described many complex implementation issues that would need to be addressed, as well as suggestions to support implementation.

We propose to conduct a clinical trial of CAB-LA as PrEP in Australia using an implementation science framework. Implementation science aims to understand how to best implement evidence-based interventions or products, identify barriers and facilitators to successful implementation, and measure how well implementation occurs. We propose to examine some research questions focused on implementation (e.g. acceptability, feasibility, appropriateness, adoption, cost, and satisfaction) and also focus on the effectiveness, safety, and clinical characteristics of CAB-LA in real-world settings (e.g. safety, effectiveness at preventing HIV infection, drug resistance, incidence of sexually transmitted infections, "breakthrough" HIV infections, and adherence). The overall objectives of the trial would be to: 1) Assess the effectiveness, safety, and clinical outcomes of CAB-LA as PrEP in eligible participants; and 2) Determine the best way/s to implement CAB-LA as PrEP in the Australian context.

We propose to utilise a mixed-methods approach to data collection and to collect data from two types of study participants: patients who receive CAB-LA injections, and clinical staff involved in the implementation of CAB-LA.

Our aim is for this trial to reflect what real-world implementation of CAB-LA as PrEP would look like under the Pharmaceutical Benefits Scheme (PBS). Since there is already a low-cost and effective form of oral PrEP available on the PBS in Australia, it is unlikely that the Pharmaceutical Benefits Advisory Committee (PBAC) will approve CAB-LA as PrEP for everyone who wants it unless it is made available at a similarly low price. We believe CAB-LA will likely initially be positioned as a PrEP option for those who are unable to take or who struggle to take oral PrEP. We propose that to be eligible for CAB-LA, patients should be considered suitable for PrEP based on HIV risk eligibility criteria outlined in the National PrEP Guidelines, **and** in whom oral TDF/FTC PrEP is medically contraindicated (e.g. due to renal or bone toxicity), **and/or** considered to be at risk of HIV acquisition if CAB-LA was withheld, such as due to difficulties with adherence to oral PrEP.

In this Discussion Paper, we outline several challenges, questions or issues related to CAB-LA implementation that we may want to explore in the context of a trial. These include:

- How “real-world” should this trial be?
- Will CAB-LA be likely to be rolled out as an optional “niche” PrEP product or will it have more general applicability?
- Which implementation issues should be the primary priority of the trial, which should be explored as secondary issues, and which should not be explored?
- What strategies should we put into place to support clinics and patients to implement CAB-LA? Examples could include: training, information materials, audit and feedback, enhanced follow-up strategies including technological solutions, visit simplification measures, and tools for quality monitoring.
- How should clinic visits be managed and who should administer the injections?
- What should be the protocol for HIV testing in the trial, and can we identify a method to allow same-day initiation of CAB-LA injections as we currently have with oral PrEP? For example, could we consider using rapid antibody/antigen HIV tests in parallel with laboratory HIV tests? Should we involve any HIV RNA testing in the trial?
- How should we manage STI testing schedules, given that CAB-LA injections need to be given 6 times per year and STI testing is recommended quarterly?
- How should clinics and patients manage the injection window of 7 days before and 7 days after the scheduled injection date, as well as planned and unplanned missed injections?
- What should be the protocol for discontinuing CAB-LA (or switching to oral PrEP), given the long pharmacokinetic “tail”?
- How should we manage dispensing of CAB-LA injections (i.e. from pharmacies, from clinics)? Should patients be required to pay for drug in the study, at the PBS price?
- How should patient and community messaging be designed?
- Could we explore the potential for self-injection of CAB-LA, perhaps in a sub-study?

We are seeking the assistance of members of the Australian HIV sector to explore these issues in more depth, prioritise them, and consider issues of study design.

Part I. Background

Introduction

Pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention option that has revolutionised HIV prevention in Australia.[1, 2] Oral PrEP is currently available in Australia, as a co-formulated single tablet of Tenofovir (TDF) and Emtricitabine (FTC), which can be taken daily or using an "on-demand" regimen (two tablets 24 to two hours before an anticipated sex act, followed by a daily tablet every 24 hours until 48 hours after the last sex act). The current National HIV Strategy has a target of 75% of PrEP-eligible people on PrEP, while the NSW HIV Strategy aims for 90% of men who have condomless sex with male casual partners to be on PrEP.[3, 4] Recent estimates suggest about 65-69% of gay and bisexual men (GBM) reporting condomless sex with casual partners are taking PrEP.[5, 6]

To achieve a higher level of PrEP use in at-risk people, and to provide consumer choice, new long-acting PrEP modalities are being investigated. Long-acting forms of PrEP can reduce the risk of non-adherence by enabling the controlled release of PrEP over an extended duration of time to prevent HIV-1 infection.[7] The only of these yet to be proven effective in Phase III randomised clinical trials is long-acting injectable Cabotegravir (CAB-LA).[8, 9] Cabotegravir is an integrase strand transfer inhibitor, and when used as PrEP, is injected intramuscularly into the buttock of confirmed HIV-negative individuals at a dose of 600mg/3mL, four weeks apart for the first two injections and every eight weeks thereafter.[10] CAB-LA was approved by the United States (US) Food and Drug Administration (FDA) in December 2021 for use as HIV PrEP in-at risk adults and adolescents.[11] In July 2022, it was recommended by the World Health Organisation (WHO) to 'be offered as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches'.[10] In August 2022, the Australian Therapeutic Goods Administration (TGA) approved CAB-LA as PrEP, with the brand name Apretude, and thus Australia became the second country globally with regulatory approval.[12] This will likely be followed by a submission to the Pharmaceutical Benefits Advisory Committee (PBAC) for public subsidy on the Pharmaceutical Benefits Scheme (PBS), although the timing of this is currently uncertain.

The availability of CAB-LA as PrEP in Australia (along with other long-acting modalities currently being studied in clinical trials) will offer an important choice to those at HIV acquisition risk for whom oral PrEP has not been a viable option and could plausibly increase the number of people using PrEP, thereby bringing Australia closer to the national goal of virtually eliminating HIV transmission by 2030.[3]

To prepare for the likely introduction of CAB-LA in Australia, researchers from the Kirby Institute at UNSW Sydney and Alfred Health in Melbourne have been funded by ViiV Healthcare and NSW Health to conduct a range of activities to determine research priorities and potential implementation issues, consult with stakeholders in the Australian HIV sector, and develop a protocol and funding application for an implementation science trial. Four primary activities have been conducted or are currently being conducted (Figure 1):

1) A scoping literature review of all published literature on CAB-LA specifically and long-acting PrEP modalities generally;
2) A survey on values and preferences about PrEP among Australian gay and bisexual men (GBM);
3) Qualitative interviews with HIV sector stakeholders and clinical service providers; and
4) Co-design workshops with PrEP users and potential users, and separately with clinical service providers.

This Discussion Paper summarises the findings of these activities to date, and describes a range of complex implementation issues that could be explored in a research trial.

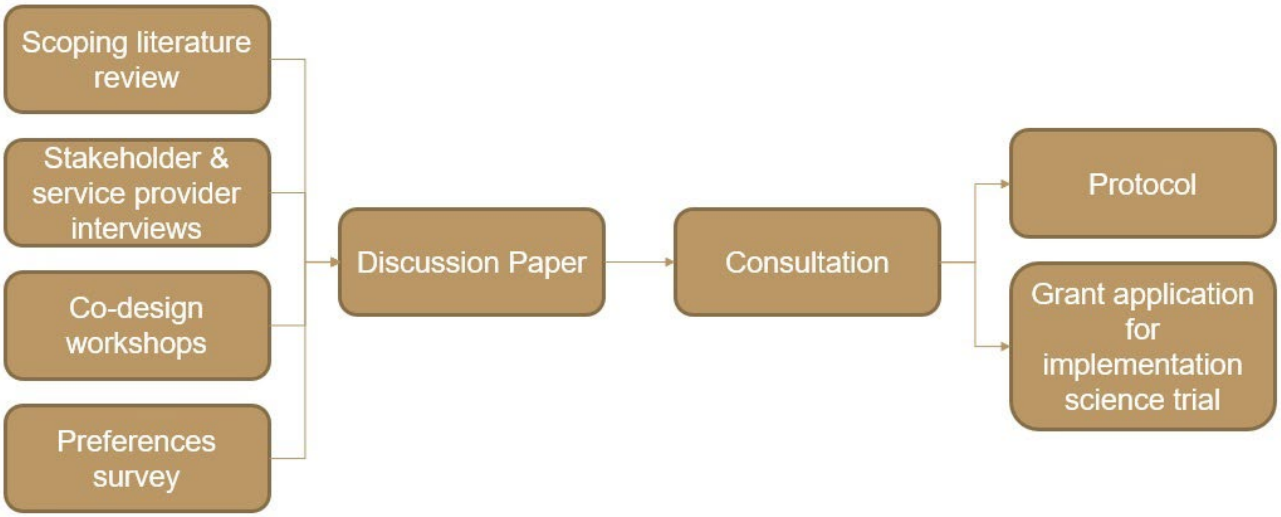

Figure 1. Process and activities to determine research priorities for CAB-LA implementation research in Australia.

Clinical trial evidence

Two large-scale randomised clinical trials have been conducted to examine the efficacy of CAB-LA as PrEP. *HPTN083* was a randomised, double-blind, double-dummy, noninferiority trial that compared the efficacy of CAB-LA (600mg/3mL injected intramuscularly every eight weeks) with daily oral TDF/FTC PrEP in at-risk cisgender men who have sex with men (MSM) and transgender women who have sex with men in sites across the US, Latin America, Asia, and Africa.[8] *HPTN084* was a randomised, double-blind, double-dummy, active-controlled, superiority trial that evaluated the safety and efficacy of CAB-LA (600mg/3mL injected intramuscularly every eight weeks) compared to daily oral TDF/FTC for PrEP in HIV-uninfected women in sub-Saharan Africa.[9] In 2020, both trials were stopped early after demonstrating efficacy outcomes had been met and that CAB-LA was superior to daily oral TDF/FTC.[8, 9] *HPTN083* found that the CAB-LA arm had a 66% relative risk reduction compared to daily oral TDF/FTC, while *HPTN084* found an 88% risk

reduction.[8, 9] Both these studies confirmed that CAB-LA is well tolerated, has an acceptable safety profile, and can increase adherence, thus reducing HIV risk among cisgender MSM and heterosexual women (cisgender and transgender).[8, 9]

In both studies, injection site reactions were the most common adverse event reported by participants in the CAB-LA arms (81% and 38% for *HPTN083* and *HPTN084*, respectively), contributing to 2.4% of participants discontinuing in *HPTN083* and zero in *HPTN084*.[8, 9] In *HPTN084* there were 29 confirmed pregnancies in the CAB-LA group and no neural tube defects or other congenital anomalies were observed.[9]

While HIV acquisitions during *HPTN083* and *HPTN084* were low, there have been concerns about the sensitivity of HIV antibody and antibody/antigen testing as there were several delayed detections of HIV infection. Delayed detection of HIV infection can occur in people taking PrEP because the drug/s can partially suppress viral replication leading to delayed antibody expression. Delayed detection is a concern because it may lead to patients continuing to receive CAB-LA injections after acquiring HIV, which increases the risk of potential drug resistance, because of the delay in initiation of a fully suppressive three-drug treatment regimen.[13] In some settings, HIV infection may have been detected earlier if a more sensitive viral load assay was used (i.e. RNA testing).[13] The US Centre for Disease Control and the US FDA have require HIV RNA testing prior to Cabotegravir initiation and at the time of every CAB-LA injection.[14] By contrast, the recent WHO CAB-LA PrEP guidelines do not recommend mandatory RNA testing and state that the potential public health benefits of including RNA testing as part of testing strategies and algorithms for CAB-LA initiation/monitoring remain unclear.[10] The guidelines recommend that HIV testing be conducted according to the relevant local or national HIV testing strategy and algorithm.[10] However, it is suggested, where feasible, RNA tests may be used in addition to national algorithm testing requirements as they may prevent a small number of cases of drug resistance.[10]

CAB-LA has a long half-life which allows for long-acting protection.[15] While offering the advantage of ongoing protection, this also increases the length of time the drug remains in the body after a final injection, known as the pharmacokinetic “tail”.[16] In a secondary analysis of *HPTN077*, the estimated mean time from final injection to below the lower limit of quantification was 43.7 (range 20–153) weeks for males and 67.3 (range 18–226) weeks for females.[17] Being assigned female at birth and having a higher body mass index (BMI) were associated with longer duration of detectable CAB-LA concentrations.[17]

There were 16 HIV infections in men who have sex with men or trans women in the Cabotegravir arm in *HPTN083*; four of these were due to undetected HIV infection at enrolment (known as baseline infection) and 12 were identified as incident HIV infections. Of the 12 incident HIV infections, five occurred in participants with no recent exposure to oral or injectable Cabotegravir; three occurred during the oral lead-in; and the remaining four HIV infections occurred in participants who had on-time injections and the expected drug concentrations in plasma.[8, 13] It is unknown why these infections occurred. It is important to recognise that such “breakthrough” HIV infections were very rare (i.e. 0.18% of participants in the CAB-LA arm of the trial). A total of five integrase strand transfer inhibitor (INSTI) resistance mutations were identified; one in a participant identified as a baseline infection, and in a further four out of nine incident cases that had drug resistance testing.[8] Of the five people with INSTI resistance, the participant identified as a baseline infection case developed INSTI resistance after receiving one CAB-LA injection, the two participants who acquired HIV during the oral lead-in period had developed INSTI resistance at the first viremic visit after receiving a CAB-LA injection, and the two remaining cases were identified in

participants who acquired HIV despite on-time CAB-LA injections and INSTI resistance was detected after four CAB-LA injections.[13] In *HPTN084*, there were four incident HIV infections in women in the Cabotegravir arm. Two infections occurred during the oral lead-in due to non-adherence.[9] The remaining two infections occurred in participants who received CAB-LA injections; one participant had three delayed CAB-LA injections, and both had been non-adherent to oral Cabotegravir.[18] Among these four incident HIV infections, there were zero INSTI resistance mutations identified.[9]

Analysis of CAB-LA drug concentrations in a subset of transgender women with and without gender-affirming hormonal therapy participating in *HPTN083* found that CAB drug concentrations were comparable between the two groups, suggesting that gender-affirming hormones have no impact on CAB-LA concentrations.[19]

The Australian registered product information for CAB-LA states that the time to onset of protection after commencing CAB-LA injections is unknown.[18] This is likely to be an issue of concern for potential users of CAB-LA.

TGA approval

The TGA approved CAB-LA as PrEP, under the brand name Apretude, on 11 August 2022. Key details from the registered product information include:

- There is no requirement for RNA testing prior to initiating CAB-LA and while receiving injections.
- Individuals must have a documented HIV-negative test “in accordance with applicable guidelines” before initiating CAB-LA.
- Oral lead-in with Cabotegravir tablets is optional. If a patient elects to initiate CAB-LA with the oral lead-in, tablets should be taken daily for at least 28 days prior to the first injection to assess tolerability.
- With oral-lead in, the schedule is daily oral tablets for at least 28 days (month one), with the first CAB-LA injection on the last day of oral tablets or within three days thereafter (month two), the second injection one month later (month three), followed by injections two months later (month five) and two-monthly thereafter.
- Without oral lead in, the first injection is given (month one), followed by the second injection one month later (month two), followed by an injection two months later (month four) and two-monthly thereafter.
- Injections should be administered up to seven days before or seven days after the date of the scheduled injection.
- Injections should be administered by an (undefined) “healthcare professional”.
- HIV testing should be conducted at least every three months while the patient is receiving CAB-LA injections.
- Daily oral Cabotegravir tablets can be used to cover one planned missed injection.
- If there are unplanned missed injections (or there are two or more planned missed injections), the initiation process must start again (unless covered by daily oral tablets during the entire period).

- Alternative forms of PrEP should be considered following discontinuation and should be initiated within two months of the final CAB-LA injection (i.e. at the time when their next CAB-LA injection would have been due).

Summary of our findings

In this section, we will briefly summarise the methods and key findings of our four research activities to date.

Scoping literature review

Description and methods

In April 2022, we conducted a scoping review to identify and summarise published data on long-acting injectable (LAI) PrEP and CAB-LA relating to acceptability, willingness, preferences, and implementation. Using PubMed and Google Scholar, 402 records were screened, and 121 records were included in the final review.

Findings

Recent studies among key priority populations within the HIV response globally have shown high levels of interest[20-30] and willingness[31-52] in using LAI PrEP.

In Australia, one study conducted in 2019-20 among PrEP-experienced GBM found high interest (59.7%) in LAI PrEP, with 30.5% selecting it as their top preference; for both interest and top preference, LAI PrEP was the most highly rated modality.[28] The *PrEPARE Project* asked similar questions of a general sample of GBM in 2019 and again in 2021. In 2019, 50.1% of current PrEP users and 32.7% of non-PrEP users preferred LAI PrEP, and it was rated highest in both groups.[53] In 2021, a new response option (monthly oral pill) was added. Among PrEP users, monthly pills (30.5%) and LAI PrEP (29.2%) were the equal most preferred, whereas in non-PrEP users, monthly pills were rated highest (30.9%), followed by on-demand oral PrEP (23.4%), and then LAI PrEP (21.0%).[54]

Preference data globally has shown that common reasons key priority populations prefer LAI PrEP include: easier alternative to a daily oral pill;[22, 25, 28, 34, 55-65] convenience and ease of use;[34, 55-58, 62, 66-69] efficacy and improved adherence;[47, 55, 60, 63, 66, 69-74] privacy and discreteness;[25, 59, 60, 63, 66, 68, 69, 73] dosing frequency;[34, 55, 57, 58, 61, 63, 66, 73] and route of administration (including disliking pills and not wanting to take pills if they are not sick).[47, 59, 60, 65, 75, 76] The most common barriers to LAI PrEP included: fear/dislike of needles;[34, 38, 47, 49, 55, 60, 66, 69, 77] fear of pain from injections;[22, 38, 60, 67, 73] concerns of side effects;[38, 55, 60, 67, 69, 70, 75, 78] logistical difficulties with clinic appointments;[34, 38, 49, 55, 70, 78, 79] fear PrEP efficacy may wane before next appointment;[34, 47, 49, 78, 80] and prohibitive costs.[49, 70, 78, 79] Additional data available on LAI preferences have revealed other insights including: the location of the buttock injection may not be ideal for users;[67, 74] while current injection dosing frequency (every eight weeks) was acceptable, options for longer duration were preferable;[38, 47, 58,

[60, 65, 70, 75, 78] receiving injections in clinics was acceptable,[38, 59, 64, 79, 81, 82] however the product needs to be widely accessible and available;[64, 79, 81, 82] self-injection is preferred by some;[55, 70] and costs need to be low/equal to oral PrEP.[40, 56]

Given that CAB-LA has only recently been proven efficacious, and other forms of LAI PrEP are still not proven, few acceptability studies have been performed to date. Of six clinical trials that studied acceptability based on lived experience, all demonstrated that satisfaction, acceptability, willingness to continue or use in the future, and willingness to recommend CAB-LA to others was generally high.[83-90] While there are limited data available on real-world experience using CAB-LA as PrEP, findings from implementation science trials of two-drug LAI antiretroviral therapy (ART) using Cabotegravir and Rilpivirine injections can provide useful implementation learnings for CAB-LA as PrEP. Within the *CUSTOMIZE* trial, overall healthcare staff found LAI ART acceptable, appropriate, feasible and sustainable to implement across diverse US clinic types, with most feeling that optimal implementation was achieved in one to three months.[91] Patients reported minimal barriers to receiving LAI ART and 94% preferred LAI ART over oral dosing.[91] A European companion study to *CUSTOMIZE* called *CARISEL* is currently collecting data and results will build on the body of evidence collected by *CUSTOMIZE* and should be released in late 2022 or 2023.

A number of global experts in the HIV field have explored expected implementation considerations for LAI PrEP including: introducing strategies to adopt flexible modes of delivery and simplification of LAI administration;[57, 92-96 23, 95, 97-102] defining strategies, policies, and collaboration;[16, 69, 95, 96, 99, 100, 103-109] addressing complexities of drug resistance and the pharmacokinetic tail;[16, 92, 94, 95, 98, 99, 104, 110, 111] high-level planning for clinical support required;[87, 95-97, 99, 101, 104, 105, 112-115] prescribing and operational considerations for clinicians and clinics;[97, 101, 116-118] manufacturing logistics;[92, 98, 104, 112, 119, 120] addressing systemic barriers for consumers;[96, 98, 100, 112] and the necessary future research requirements.[16, 87, 91, 96, 98-100, 103, 104, 107, 108, 110, 112, 113, 115, 118, 121-124]

Quantitative survey among GBM

Description and methods

We conducted an online, cross-sectional survey open to gay, bisexual, and other men who have sex with men (GBM) from June to August 2022. The survey was designed in collaboration with an international team of researchers, policymakers and community organisations and was concurrently conducted in 15 Asian countries. The overarching aim of the survey was to explore the values and preferences held by GBM about PrEP, including preferences for current and future PrEP options, attitudes, PrEP knowledge and experience, and a series of specific questions about CAB-LA. The survey included a discrete choice experiment (DCE) examining preferences regarding preferred types of PrEP, cost, preferred access location, side effects and medicine interactions, frequency of prescriptions/clinical visits, and other services that can be combined with PrEP services. In Australia, the survey and advertising materials were presented in English, Thai, Vietnamese, and Simplified Chinese. It was promoted via advertisements on social and sexual networking websites and applications, including Grindr, Hornet and Facebook, as well as to email lists of participants of previous Kirby Institute studies.

Demographic characteristics

The total sample consisted of 1608 participants who lived in Australia. The average age was 40.4 (SD=12.7), and most were recorded male at birth (n=1585, 98.6%), identified as a man (n=1557, 96.8%), and identified as either gay (n=1239, 77.1%) or bisexual (n=279, 17.4%). About a quarter (n=446, 27.7%) were born in a country outside of Australia, most commonly from within Asia (n=126, 28.3%), followed by New Zealand (n=60, 13.5%), and the United Kingdom (n=50, 10.6%). Over half (n=877, 54.6%) had a university degree, and over two-thirds (n=1097, 68.4%) were working full-time.

Findings

PrEP awareness and use

Nearly all participants were aware of PrEP (n=1543, 96.0%). Participants most commonly reported being aware of daily PrEP (n=1425, 88.6%) and then on-demand PrEP (n=1171, 72.8%), with one-fifth having heard of CAB-LA (n=338, 21.0%). The survey used the term “long-acting PrEP injections every 2 months (‘Cabotegravir’)”.

Nearly two-thirds of participants had taken PrEP (n=1021, 63.5%). Of the total sample, 44.6% were currently taking PrEP (n=717), with a further 13.3% having stopped temporarily (n=213) and 5.6% participants having stopped permanently (n=90). Among the 717 participants currently taking PrEP, most were taking it daily (n=540, 75.6%), with one-quarter taking on-demand PrEP (n=168, 23.5%).

Reasons for not initiating PrEP or stopping PrEP

Among participants who had heard of PrEP but have not taken it (n=522), two-thirds (n=334, 64.5%) said they would like to take PrEP but had not. Among these 334 participants, the most common (non-mutually exclusive) reasons that they did not initiate PrEP included not having much sex (n=131, 39.2%), not knowing where or how to get PrEP (n=118, 35.3%), concerns about side effects (n=100, 29.9%), and believing it was too expensive (n=77, 23.1%).

Among participants who had previously taken PrEP but had either stopped temporarily or permanently (n=303), the most common (non-mutually exclusive) reasons were that they were not having much sex (n=139, 45.9%), they entered a monogamous relationship (n=92, 30.4%), concerns about side effects (n=55, 18.2%), and cost (n=49, 16.2%).

Interest and preference

We asked participants to consider several PrEP modalities and to answer questions about their interest in and top preference for the modalities assuming that all were available and equally effective in providing protection against HIV infection. This list included potential future PrEP options, such as a monthly oral pill, a 6-monthly injection, and a removable implant lasting up to one year. When asked what modalities participants were interested in using, the most popular modalities were the monthly oral pill (n=999, 62.1%), the 6-monthly injection (n=820, 51.0%), daily oral dosing (n=671, 41.7%), on-demand oral dosing (n=579, 36.0%), a removable implant (n=547, 34.0%), and a 2-monthly injection (n=406, 25.3%). A small number of participants were not interested in using any modality (n=61, 3.8%).

Participants who selected more than one option on the question above were asked which would be their top preference; participants who only chose one were assumed that this choice was their top preference. The most preferred modalities were the monthly oral pill (n=428, 26.6%), the 6-monthly

injection (n=379, 23.6%), the removable implant (n=241, 15.0%), daily oral dosing (n=212, 13.2%), on-demand oral dosing (n=206, 12.9%), and the 2-monthly injections (n=60, 3.7%).

It is important to note that while 2-monthly injections were not rated highly in comparison to other, hypothetical long-acting modalities, there was high interest overall in long-acting forms of PrEP. Until other modalities become available, it is likely that many Australian GBM would like to use CAB-LA as PrEP given that the currently available oral modalities were not preferred.

Potential benefits and concerns about CAB-LA

When asked to select from a list of potential reasons why CAB-LA could be an attractive option, the most common (non-mutually exclusive) reasons were not having to remember to take pills (n=1056, 65.7%), the protection it offers from HIV (n=1035, 64.4%), the fact it may offer long-term protection compared to other methods (n=764, 47.5%), and not having to take oral pills (n=670, 41.7%).

When asked to select from a list of concerns about CAB-LA, the most common (non-mutually exclusive) concerns included that they did not know about it (n=761, 47.3%), that the potential cost may be unaffordable (n=731, 45.5%), side effects (n=524, 32.6%), and not liking injections (n=442, 27.5%).

Participants said they would consider trying CAB-LA if it had higher effectiveness than oral PrEP (n=1227, 76.3%), had fewer side effects than oral PrEP (n=1048, 65.2%), or had lower drug toxicity than oral PrEP (n=888, 55.2%).

Participants would most like to be administered CAB-LA in a sexual health clinic (n=617, 38.5%), at a general practice clinic (n=537, 33.5%), or to be trained to administer it at home (n=245, 15.3%).

Qualitative interviews with service providers and stakeholders

Description and methods

We conducted 27 semi-structured interviews with PrEP service providers and stakeholders between March and September 2022. Interviewees consisted of a range of service providers and stakeholders in Australia involved in the provision or implementation of PrEP including nurses, general practitioners (GPs), sexual health clinicians, pharmacists, researchers, policymakers, non-government and community organisation staff members, and activists.

Findings

Considerations for patients

Most service providers and stakeholders were largely in favour of CAB-LA for its capacity to provide an alternative to oral PrEP and it was viewed as an opportunity to increase PrEP uptake and destigmatise PrEP use among people who had previously never used PrEP due to perceptions of stigma. CAB-LA was suggested as a suitable alternative to oral PrEP for the following specific end-users:

- those with an existing contraindication to PrEP (e.g. impaired renal function; low bone mineral density)
- those who have experienced side effects from oral PrEP (e renal impairment; persistent gastro-intestinal symptoms);
- those who have difficulties adhering to oral PrEP; or
- those who would find injections more convenient and/or those who require discretion, such as users who live in or travel to places where HIV might be stigmatised (i.e. where pill visibility may be a concern).

Service providers and stakeholders also acknowledged that other populations may be interested in CAB-LA such as those who already use oral PrEP and who had little difficulty adhering to it but would be interested in switching to CAB-LA or using CAB-LA for periodic use during a season of higher sexual risk or while travelling (for less than 2 months).

The increased burden associated with attending six clinical appointments per year was raised as well as secondary financial impacts of clinic costs, travel costs, and unpaid time off work to attend appointments. The complexities for equitable access were raised as despite holding the potential to increase uptake for people who might struggle with oral PrEP due to their complex circumstances, CAB-LA may not be suitable for those who cannot engage regularly with services. In addition, other inequitable access issues may arise for Medicare-ineligible patients who will not have access to PBS-subsidised PrEP and may not be able to import CAB-LA from overseas.

Service providers and stakeholders held concerns about communicating breakthrough infections and the complexity of the pharmacokinetic tail, and emphasised that appropriate and responsible framing to the community will be required.

Stakeholder perspectives

HIV sector stakeholders expressed some ambivalence around the introduction of CAB-LA and what this would mean for community. Concerns were raised that CAB-LA messaging may frame injectable PrEP in a deficit way (i.e. those who cannot take oral PrEP) and that there is potential for injectable PrEP to represent (re)medicalisation of PrEP services, as it requires administration within a clinic. The potential of self-administrating CAB-LA was strongly suggested as a way to reduce stigma and increase empowerment.

Stakeholders also suggested that CAB-LA should be available for cisgender women and trans men at risk of HIV given the higher adherence requirement for oral PrEP to provide protection against HIV transmission through vaginal/front hole sex. In addition, they suggested it be available for people who engage in an ongoing way in chemsex (however this group may be conceptualised with the general grouping of non-adherers).

Participants also wanted to know more information about the “experience” of actually taking CAB-LA and the implications of taking a “long-acting” and injectable agent.

Lastly, considerations about whether CAB-LA will provide more choice were raised. Stakeholders were enthusiastic about long-acting and injectable PrEP technologies, but were ambivalent towards the CAB-LA drug itself.

Challenges to implementing CAB-LA in services

Service providers and stakeholders raised multiple challenges to implementing CAB-LA in services, particularly as the six appointments per year needed with CAB-LA may increase the burden on resource capacity within clinics. Ensuring patients return for appointments within the two-week window is likely to be resource intensive, and appointment processes could be more complex. Ambivalence about HIV and STI testing requirements was commonly raised and participants expressed mixed sentiments about testing schedules. Some participants stated that conducting tests at every CAB-LA injection (six tests per year) was feasible and appropriate, some stated that the current HIV testing model of four tests per year should be maintained, and some stated that fewer HIV tests should be conducted, such as at every second visit (three tests per year). Implementing fewer HIV tests was seen to have benefits for reducing long-term burden on services and reducing burden on the user. Some participants suggested that all STI testing should remain coupled to HIV testing (whether that be six, four, or three tests per year), some suggested that fewer STI than HIV tests should be conducted, and some suggested that HIV and syphilis tests should be conducted together and decoupled from gonorrhoea and chlamydia testing.

Participants suggested the following potential added resources and/or costs to services that would be required to implement CAB-LA, including:

- Testing: increased HIV and STI including staff and/or time for conducting increased pathology.
- Injections: injection equipment, staff and/or time for injections, staff and/or time and/or medical products to address adverse injection reactions.
- Clinical assessment: length of initial appointment.
- Scheduling and follow up: Staff and/or time for follow up, scheduling and rescheduling.

Suggestions to support implementation

Participants provided a range of suggestions to support CAB-LA implementation. Most service providers noted they already had, or could modify their services to have, the resources available to implement CAB-LA. Redeveloping current PrEP follow-up systems to allow future follow-up management for CAB-LA was commonly suggested by service providers as well as incorporating a systemic/team approach to implementing CAB-LA and providing opportunities to support clinician training. Some additional suggestions for improving follow-up included escalating users who miss appointments to priority appointments, conducting more rigorous recall beyond text messages and emails to ensure the user attends appointments, and modelling a more rigorous follow-up system off those used for current long-acting treatments.

Most service providers and stakeholders were in favour of innovative models of care such as nurse-led, peer-led, and pharmacy-led models. These models may have capacity to improve the user experience and provide greater access, reduce burden on services, and/or allow for greater use of task-shifting to trained and skilled staff.

Use of digital technologies to support appointments and scheduling was commonly raised, such as telehealth to receive results, and/or providing e-scripts and digital pathology forms to users prior to injections so they could avoid attending in-person appointments. Participants suggested that digital services such as phone apps, an opt-in or opt-out texting service, and peer-led follow up services could be used to remind users of upcoming appointments, follow up missed appointments, and provide general information and support about CAB-LA, PrEP, and sexual health. My Health

Record was also suggested by some providers as a platform for mobile CAB-LA users who frequently travelled interstate and might need to attend difference services.

Co-design workshops

Description and methods

We undertook a series of co-design workshops with end-users and potential end-users of long-acting, injectable PrEP (and other, future PrEP technologies). To date, we have also conducted one co-design workshop with PrEP service providers. This methodological approach draws on participants' interests, concerns, and lived experience in order to identify issues likely to have an impact on the acceptability and adoption of these new technologies. This approach complements other research that investigates stated and/or observed preferences (based on calculations of cost, effectiveness/efficacy, frequency of dosing/administration, etc), by integrating intuitive/emotional attributes and social/relational factors into the exploration of these questions.

Findings of end-user workshops

To date, three of the planned end-user workshops have been conducted (total 32 participants). All participants have been gay, bisexual and/or queer identifying men (including trans men). Participants' mean age was 35 years. Most were current PrEP users (although some had never taken PrEP, and others were previous PrEP users). The majority described their cultural/ethnic background as Australian and/or West or Southeast European, with others identifying as Indian, Persian, Brazilian, African-Caribbean, or Aboriginal Australian.

Participants identified a range of *product attributes* as well as *social/relational factors* specific to end-users' circumstances likely to influence interest in – as well as acceptability and uptake of – CAB-LA. These insights indicate relevant factors in terms of: 1) predicting likely users of injectable PrEP; 2) identifying areas on which to focus messaging/information about this form of PrEP; and 3) recognising feasibility issues related to implementation that need to be further investigated (including as part of a potential implementation project).

Participants described several reasons why people might prefer or choose injectable PrEP over the current oral PrEP options:

- Cultural beliefs and preferences about mode of administration:
    - Beliefs about injections over pills (including potency, absorption/take-up in body);
    - Associations of injections with prevention (compared to the association of pills with treatment);
    - Complementing cultural/religious practices (e.g. Ramadan).
- Privacy/discretion:
    - Ability to hide PrEP use from others (partner, family, household members), which might be especially relevant in some settings (Aboriginal communities; regional settings; non-gay-identifying MSM; women; and within some specific culturally and linguistically diverse [CALD] settings).
- Personally identifying as an "early adopter", and therefore being someone who is attracted to new technologies.
- Inability to tolerate the adverse effects of current oral PrEP formulations.

- Persistent experience of side-effects from oral PrEP formulations.
- Concerns and beliefs about the toxicity of oral PrEP (especially over a projected period of many years).
- Travel:
    - Convenience;
    - Specific countries where same-sex contact is punishable.
- Adherence issues:
    - CAB-LA involves minimal day-to-day responsibility on the part of the user (in terms of adherence);
    - Allows for variation in regular routine, and more "spontaneity";
    - Removes the need to go home to get pills (including in chemsex contexts).
- Less "anxiety" (related to reducing the burden of adherence to oral doing schedules; perceptions among some of greater effectiveness compared to oral PrEP, specifically in context of sex with known HIV-positive partners).
- "Flexibility" (i.e. the perceived convenience of switching to injectable PrEP as an ongoing or temporary strategy, and switching back to oral PrEP if/when circumstances change).
- The possibility of self-administration.

These insights suggest injectable PrEP may be attractive to some people who have never previously used PrEP, however, may also be very attractive – if not more so – to current PrEP users, especially when considering issues related to the drug "tail" (for which consideration of a switch/return to oral PrEP for approximately one year after the final injection is recommended).

Regarding messaging for potential end-users of oral PrEP, there is a need to raise awareness about the specific features of injectable PrEP that distinguish it from current oral TDF/FTC forms of PrEP.

Issues related to <u>starting</u> injectable PrEP:

- Uncertainty about the time to adequate/optimal drug levels after injection.
- Uncertainty about the likelihood of adverse effects from CAB-LA, and therefore questions about the need for the oral lead-in.
- Frequency of injections: the perception among participants that 8-weekly injections are not generally considered "long-acting".
- Need for further information about the details of the injections, including the size of needle, quantity, and properties of the product (including the fact it is a different drug from current oral formulations), location of injection site, and pain or injection site reactions.
- Perception that implementation study would be limited to a small number of clinics in inner-city locations.

Issues related to <u>regular (8-weekly) injection cycle</u>:

- Concerns about CAB-LA drug levels during the period immediately before the next scheduled injection.
- Flexibility around the need for 8-weekly visits:
    - The official "window" as per the registered product information regarding late and missed clinic visits.
    - The protocol for return to oral PrEP in case of missed clinic visits (including arrangements for unplanned missed visits, e.g. backup prescription or supply of Cabotegravir- or Tenofovir-based pills).

    - Willingness of providers/guidelines to bring scheduled injection visits forward to accommodate planned travel, etc.).
- Total burden on users around clinic visits and monitoring:
    - HIV testing (including frequency and the need for HIV testing prior to each injection, and whether this would require an additional clinic/pathology visit, and/or whether point-of-care or home HIV testing would be incorporated into the study).
    - How to manage the cycle of STI testing (and other pathology tests), given the 8-weekly injection schedule does not match guidelines for STI testing.
    - Requirements regarding prescription, supply, storage and dispensing of product.

Issues related to <u>discontinuing</u> injectable PrEP:

- Concerns about the drug "tail" and the need for further information.
    - Specifically, concerns about the requirement for – and whether there can be flexibility around – the recommended switch/return to oral PrEP for approximately one year after the final injection.
- Flexibility (of protocol, and of clinicians and services) in terms of allowing individuals to move frequently between injectable and oral options, i.e. is there a limit?

Findings of service provider workshop

A healthcare provider workshop was held in Melbourne. The healthcare providers who attended included doctors, nurses, and pharmacists.

The attendees were pleased that another PrEP option could become available to some of the population, but were concerned that it would be hard to identify people who were not able to tolerate oral PrEP, or who had adherence issues to oral PrEP. Also, although intolerance to current oral formulations was acknowledged, other adverse effects were considered a negligible issue (the group was almost unanimous on this point). It was acknowledged that some people experienced side effects when starting PrEP but these effects almost always resolved soon after.

The clinicians stated that they would have to do a practice audit to identify people who were no longer attending for PrEP, or who had ceased PrEP due to side effects. GP practices, in particular, do not have the capacity to audit patient records to identify those who are: lost to follow up; missed multiple appointments; without valid current prescription or pill supply; discontinuers; or have moved to other clinic (or state/territory). This inability is partly related to the patient management software, which makes it difficult to identify cancelled appointments. (Also, the increase in people taking event-based PrEP has also made it difficult to estimate overall non-adherence among patients.) They expressed the view that a research study would need to pay clinics to undertake audits. Furthermore, the clinicians expressed that it would be a challenge to audit whether or not patients attended for their eight-weekly injections. The attendees expressed how they are currently dealing with a high clinical load which includes diagnosis and treatment of STIs, monkeypox vaccinations, and the management of other chronic health conditions.

Participants believed that injectable PrEP would be more suited to "organised" patients. However, it was noted by some that these patients tended to work regular full-time hours, and therefore moving to injectable PrEP for these patients would therefore imply more demand for after-hours appointments.

They also noted that there is no Medicare Benefits Schedule (MBS) item number for giving an antiretroviral injection which reflects the fact that they think they would need more increased funding to roll out an extensive long-acting injectable PrEP program in their clinics. It was noted,

however, that there are MBS item numbers for Implanon NXT (numbers 14206 and 30062), which may be a model to draw on.

In terms of administering CAB-LA, some group members already had extensive experience administering Cabotegravir/Rilpivirine injections for HIV treatment. Notably, Cabotegravir was described as being much “nicer” as an injection than Rilpivirine. They believed it was straightforward for clinicians to learn. Additionally, there was wide support among participants for a sub-study of self-administration within a future implementation trial.

They also mentioned that there are precedents for innovative pricing models for medicines, such as the risk-sharing agreement with manufacturers for hepatitis C treatments.[125]

Part II. CAB-LA research in Australia

An Australian clinical trial of CAB-LA as PrEP

After a new drug has been proven efficacious in Phase III randomised clinical trials, there are typically many important research questions needing ongoing exploration. It is important to monitor for new and rare side effects and evaluate the real-world effectiveness and implementation of the drug outside of the heavily controlled, better funded, and rigorously observed clinical trial setting.

Therefore, following the recommendation in the World Health Organization's 2022 CAB-LA as PrEP guidelines,[10] **we propose to undertake Australia's first research study of CAB-LA for use as PrEP**.

In the process of planning this trial, it is important to consider how data about CAB-LA **implementation in Australia may benefit other countries**, whether they be similar to Australia (e.g. New Zealand, Canada, the UK, countries in western Europe) or very different (e.g. countries in the Asia-Pacific region).

We should also consider the **unique features of Australia** such as:

- Specifics of our health system including health workforce and structure of HIV and sexual-health services (i.e. similarities/differences to others overseas)
- System for funding medicines and healthcare (PBS; Medicare)
- Very low HIV incidence in the general population
- Decreasing HIV incidence in the key population of GBM, but disparities across subgroups in HIV diagnoses and use of PrEP
- Highly successful and low-cost oral PrEP program with high levels of PrEP use among at-risk GBM
- Being one of the few countries globally with a realistic chance to eliminate local HIV transmission by 2030
- Heterogeneous society with one-quarter of Australians having been born overseas
- High levels of literacy about HIV, sexual health and antiretrovirals among key populations
- Very high level of HIV treatment coverage among people living with HIV
- Relative to other countries, more accepting social attitudes towards people living with HIV, gay and bisexual men, sex work and so on.

Several trials focused on injectable CAB-LA as either PrEP or HIV treatment have been conducted, are underway, or are being planned.

- *CUSTOMIZE* is a Phase IIIb-hybrid III implementation study that was conducted between 2019 and 2022 to identify and evaluate strategies for successful implementation of the Cabotegravir/Rilpivirine long-acting injectable (LAI ART) regimen in the US. Initial results from *CUSTOMIZE* demonstrated that healthcare staff found LAI ART acceptable, appropriate, feasible, and sustainable to implement across diverse US clinics.[91]

- *CARISEL* is also an open-label, hybrid Phase IIIb trial evaluating implementation strategies for long-acting Cabotegravir/Rilpivirine administered every two months in select European healthcare settings. The one-year study was launched in late 2020 and spans across 18 diverse practice sites across different healthcare systems in France, Spain, Belgium, Germany, and the Netherlands. Results from *CARISEL* are yet to be released.
- *PILLAR* is a Phase IV, randomised, open-label, two-arm implementation science trial evaluating implementation strategies for CAB-LA as PrEP among CAB-LA-naïve MSM and transgender men in the US. It will run from 2022 to 2024. The primary outcomes focus on feasibility as reported by clinic staff, and will be compared across the "routine implementation" arm and the "dynamic implementation" arm.

All of these studies use an "implementation science" framework, and collect data from both patients and clinic staff. They focus on questions of the ongoing effectiveness, safety, and clinical characteristics of CAB-LA as PrEP, and also several implementation-focused questions. However, the primary focus of the studies is on implementation-related issues, assessed via data collected from clinic staff. These studies use a common implementation science trial design, whereby a range of implementation strategies for clinics are packaged into an "enhanced" arm and compared to a "standard" or "routine" arm.

Implementation science is "the study of methods to promote the systematic uptake of evidence-based interventions into practice and policy to improve health".[126] This field of research incorporates a wider scope than traditional clinical research by focusing not just at the patient level but also at the *provider*, *organisation*, and *policy* levels of healthcare.[127] We propose that our study focus on research questions and outcomes related to both **effectiveness, safety and clinical characteristics** of CAB-LA as PrEP, as well as **implementation-related issues**.

Trial design options

In this section, we outline options regarding the design of an implementation science trial of CAB-LA as PrEP in Australia, and commentary on which of these options is most practical and useful in our setting.

We propose two overall **objectives** for the study:

- Assess the effectiveness, safety, and clinical outcomes of CAB-LA as PrEP in eligible participants.
- Determine the best way/s to implement CAB-LA as PrEP in the Australian context.

We propose to collect data from two types of study participants (similar to the trials described above): **patients** and **clinic staff**. Patients will be individuals who attend the clinical sites, are assessed for eligibility for CAB-LA as PrEP, and enrol in the study. Clinic staff members working in the clinical sites may include doctors, nurses, peers, administration staff, and counselling staff.

A **mixed-methods approach** incorporating quantitative data (e.g. routinely-collected clinical records; prospectively-collected case report forms; surveys of patients and clinical service providers; checklists) and qualitative data (e.g. in-depth interviews or focus group discussions with patients and clinical service providers; open-text fields in surveys; observational field notes) is likely to be most appropriate.

Given that the implementation-related objective of this study is to determine the best ways to implement CAB-LA as PrEP, and that bedding down the implementation of a new intervention can take time, we propose that the study should last for up to two years for patients (i.e. patients receive two years of CAB-LA injections) and up to four years for clinic staff.

Trial design questions

There are several "big picture" questions about the trial design that we wish to consult the HIV sector about. These are cross-cutting in that they affect many of the more specific research questions and issues outlined below.

First, there is the question of **the degree to which we want this trial to mimic the "real world"**. Trials designed to assess the efficacy of new medicines or interventions are typically not "real-world" because they mandate many study procedures that would not be implemented in practice. Demonstration and implementation projects can mimic the real world to different degrees. For example, in *EPIC-NSW*, the procedures in clinics were kept as "light touch" as possible, but one important non-real-world feature of the study was that the drug was provided to participants for free, directly from the clinics (or close-by hospital pharmacies), and all clinic visits were no-cost (even at private GPs). By contrast, in *PrEPX*, participants were required to pay for the drug and required them to pick up the drug at designated community pharmacies, thereby making those aspects of the trial closer to the real-world situation post PBS listing.

Second, there is the question of whether CAB-LA as PrEP is likely to be initially rolled out as a more "specialist" (e.g. s100) product only provided at certain clinics/pharmacies or a product that will be as widespread as oral TDF/FTC PrEP. If CAB-LA as PrEP is initially a fairly niche product with few users compared to oral PrEP, then it is unlikely to be stocked by many pharmacies Australia-wide. This question has implications for the types of clinics we may want to involve as sites in this trial.

Third, in the sections below, we outline a range of implementation-focused issues that could potentially be explored in this trial. In this consultation process, we are seeking help from members of the Australian HIV sector to prioritise these issues in terms of importance, which may subsequently affect the study design. Depending on how important the issues are deemed to be, we can take different approaches to measuring and assessing different strategies. One approach might be taken to a particularly important research question (e.g. via randomisation), whereas a less important research question may be explored by simply observing what happens in clinics and evaluating it. We can:

- Mandate an approach for all sites and all patients, observe how well the approach was followed, and evaluate the approach without a comparator.
- Allow sites to choose an approach (potentially including real-time adaptations), observe, and evaluate by comparing groups in analysis.
- Allocate sites non-randomly to an approach, observe, and evaluate by comparing groups in analysis.
- Randomly allocate sites (cluster randomisation) and/or patients (individual-level randomisation), observe, and evaluate by comparing study arms in analysis. It may, for example, be possible to randomise one research question at the site level (e.g. an

enhanced package of implementation supports provided to the site) and another at the individual level (e.g. a specific approach to the frequency of STI testing).

Access and eligibility

Who could potentially benefit from CAB-LA as PrEP?

Potentially, anyone who is at-risk of acquiring HIV could benefit from an increase in choice in PrEP products offered by CAB-LA (and in the future, other new long-acting modalities). From our formative work described above, we have established that LAI forms of PrEP are of great interest to GBM in Australia (and potentially other at-risk populations). The types of people for whom CAB-LA could potentially be beneficial are wide-ranging, and include those who:

- Cannot take oral TDF-based PrEP due to renal and/or bone toxicity
- Have a strong preference for injections over oral medicines and hence be much likelier to initiate or re-initiate PrEP using injectable PrEP
- Struggle with oral PrEP adherence for a variety of reasons:
    - Experience ongoing side effects when taking oral PrEP
    - Can manage adherence to oral PrEP but do not like it or have to put a lot of effort into maintaining it
    - Repeatedly come off and on PrEP to manage side effects
- Need a long-acting choice due to travel or work requirements and/or stigma/discrimination
- Belong to populations at-risk that have not been strongly targeted for oral PrEP (e.g. at-risk women, sex workers, people who inject drugs, prisoners, Aboriginal and Torres Strait Islanders)
- Live in areas without ready access to pharmacies dispensing oral PrEP (but who could potentially travel for 8-weekly injections)
- Currently take PrEP with ongoing HIV risk but are at risk of ceasing oral PrEP for a variety of reasons
- Do not want to think about regularly taking oral pills
- Would find injections more convenient
- Have never taken PrEP due to dislike of oral medicines or other factors
- Perceive themselves as “early adopters” and appreciate having access to new products.

However, there are some challenges related to the initial access to and potential eligibility for CAB-LA as PrEP that need to be acknowledged, discussed below.

Access

Although approved by the TGA for use as PrEP in August 2022, CAB-LA will not be immediately available in Australia (i.e. at list price). It is unclear when the manufacturer will make it available for pharmacies to purchase.

At this stage, the full price of the drug (to be borne entirely by the patient) is not yet known. In the US, the list price of one dose of Apretude is currently USD $3,700 (or USD $22,200 per year per individual, assuming six doses), equating to approximately AUD $5,500 for one dose (or AUD $33,000 for one year). Even if the list price in Australia is substantially less than this, full price CAB-LA will not be accessible to most people unless it is subsidised on the PBS.

From the outset, when considering research priorities and questions about CAB-LA implementation in Australia, it is important to acknowledge that the PBS makes decisions about public funding for new medicines in large part based on cost-effectiveness. **This will be a challenge for *all* new PrEP products that are still under patent**, including CAB-LA. We currently have a very inexpensive form of PrEP – that of oral TDF/FTC PrEP – which has been effective at reducing HIV diagnoses among GBM.[2] In obtaining PBS approval for oral TDF/FTC PrEP, PBAC advised that the maximum price it would consider to be cost-effective for the Australian Government was $2500 per year per individual.[128] Currently, assuming daily use, the per year per individual cost to the Australian Government for oral TDF/FTC PrEP is $1217 (person communication with Dr Richard Gray, 20 September 2022). In terms of out-of-pocket costs for individuals, it costs $510 per year ($42.50 per prescription), or $81.60 per year ($6.80 per prescription) for those with a concession card. For those without access to the PBS, generic oral TDF/FTC imported from overseas pharmacies costs as little as $180 to $228 out-of-pocket per year per individual, assuming daily use.

The costs described above, for both government and out-of-pocket costs for individuals, are for the drug only and do not include costs associated with healthcare, such as for tests (HIV, STIs, eGFR, hepatitis B) and consultations (i.e. at GPs). Some of these healthcare-associated costs are borne by the patient (e.g. GP gap payment for Medicare-eligible individuals; full cost of consultation and tests for non-Medicare-eligible individuals), sometimes by state/territory governments (e.g. all services at publicly-funded sexual health clinics), and sometimes by the Australian Government (e.g. consultations and tests covered by Medicare). It is important to keep these funding structures in mind, and the potential costs for different subgroups of PrEP users (e.g. those ineligible for Medicare), when considering the future implementation of CAB-LA, especially given the requirement for more frequent prescriptions, clinic visits, and potentially tests than required for oral TDF/FTC PrEP.

Due to there already being such a low-cost form of PrEP available in Australia, it is unlikely that PBAC will initially approve the subsidy of CAB-LA as PrEP for everyone who wants it. Approval will depend on several factors including the proposed list price put to PBAC by the drug manufacturer, cost-effectiveness analyses conducted by PBAC and others, whether or not CAB-LA is proposed to be restricted to specific subgroups of the broader populations at-risk of HIV infection, and whether this approach is deemed cost-effective at the proposed list price. At least initially, it is likely that CAB-LA will be proposed as a PrEP option for people who are unable to take oral PrEP, with PBS subsidy restricted to a subset of people who would actually want it, measured by their inability to effectively utilise oral PrEP. This may change over time as other PrEP options that are currently in the advanced stages of the research pipeline (e.g. six-monthly injections) become licensed in Australia.

These questions of who may and may not have eventual access to CAB-LA as PrEP under the PBS are critical to the approach we take to an implementation trial. An important ethical consideration for clinical trials is that post-trial access to the drug for any participants who may

wish to continue using it is assured. We will need to carefully consider this when making decisions about trial eligibility.

CAB-LA eligibility

While we may wish for CAB-LA as PrEP to be available at a subsidised price for anyone at-risk of HIV infection who wants to use it, our research team believes that a more realistic and pragmatic approach will be to consider CAB-LA as a "second-line" form of PrEP. This represents the first time in Australia that we have had to consider PrEP in this way, although it is not too dissimilar to how oral PrEP was first introduced (i.e. restricted in some jurisdictional guidelines to the highest-risk individuals first, with gradual lessening of restrictiveness over time).

In broad terms, this would mean access to CAB-LA would be restricted to those who cannot take oral TDF/FTC PrEP for medical reasons or those for whom withholding CAB-LA would result in a high probability of HIV infection. The challenge is to determine a set of criteria for this second group that is easily understood, easily implementable in busy clinical contexts, and able to be communicated to community, and which is also likely to be acceptable to clinicians, community, the drug manufacturer, and importantly, PBAC. As we will need to make decisions about trial eligibility prior to the drug manufacturer making a submission to PBAC, the current consultation and data collected in the trial may be able to inform PBAC processes.

We propose a two-step eligibility process, to be followed at *all clinical sites* and for *all patients enrolled in the study*, outlined below.

Criterion 1: The patient should be considered suitable for PrEP based on HIV risk eligibility criteria outlined in the 2021 ASHM National PrEP Guidelines. The HIV risk eligibility criteria are outlined separately for population group and relate to the previous three months.

Table 1. Summary of HIV risk eligibility criteria in 2021 ASHM National PrEP Guidelines.

MSM (Box 4.1, p.18)	TGD people (Box 4.2, p.19)	Heterosexuals (Box 4.3, p.20)	PWID (Box 4.4, p.21)
• CLI with regular HIV+ partner who is not on ART and/or has DVL. • Receptive CLI with any casual male partner. • Episode/s of sexualised drug use. • Diagnoses of rectal GC or CT, or infectious syphilis, including diagnosed at PrEP screening. • Episode/s of anal intercourse with broken or slipped off condom with partner of unknown HIV status or HIV+ partner	• CLI with regular HIV+ partner who is not on ART and/or has DVL. • Receptive CLI with any casual bisexual male partner of unknown HIV status. • Episode/s of sexualised drug use. • Diagnoses of rectal GC or CT, or infectious syphilis, including diagnosed at PrEP screening. • Episode/s of vaginal or anal intercourse with broken or slipped off condom with partner of unknown	• CLI (anal or vaginal) with regular HIV+ partner who is not on ART and/or has DVL. • Receptive CLI (anal or vaginal) with any casual HIV+ partner or a male homosexual or bisexual male partner of unknown HIV status. • Planned CLI in an effort to conceive with HIV+ partner (regardless of viral load).	• Shared injecting equipment with HIV+ person or gay or bisexual man of unknown HIV status. • CLI (anal or vaginal) with regular HIV+ partner who is not on ART and/or has DVL. • Receptive CLI (anal or vaginal) with any casual HIV+ partner or a male homosexual or bisexual male partner of unknown HIV status.

not on ART and/or has DVL.	HIV status or HIV+ partner not on ART and/or has DVL.		

Notes: MSM = men who have sex with men; TGD = trans and gender diverse; PWID = people who inject drugs; CLI = condomless intercourse; HIV+ = HIV-positive; ART = antiretroviral therapy; DVL = detectable viral load; GC = gonorrhoea; CT = chlamydia. Box and page numbers refer to those used in the 2021 ASHM National PrEP Guidelines.

Criterion 2: The use of oral TDF/FTC PrEP is medically contraindicated **and/or** the patient is considered to be *at risk of HIV acquisition as per the ASHM PrEP guidelines if CAB-LA were withheld*.

Contraindications to use of TDF/FTC for PrEP are defined as:

- Having an estimated Glomerular Filtration Rate (eGFR) that is well-established to be below 60 mL/min/1.73m^2, **or**
- Having low bone density, in the range of osteopenia or osteoporosis, based on a bone mineral density scan.

Individuals deemed suitable for CAB-LA as PrEP may be current oral PrEP users, former users, or people who have never taken PrEP ("PrEP naïve"). We propose to define individuals who are suitable for CAB-LA as PrEP as any individual fulfilling one or more of the criteria listed in Table 2, **and** that their clinician believes effective/adequate levels of adherence to oral PrEP will not improve or will not be possible for the patient. We seek your feedback on these proposed criteria. We may conduct implementation research (e.g. education/training aids) about these criteria.

Table 2. Suggested criteria to identify people for whom oral PrEP is unsuitable.

Criterion	Current oral PrEP users	Former oral PrEP users	PrEP naïve
Clinical history of failure to adhere or struggles with adherence to chosen oral PrEP regimen.	✓	✓	
Clinical history of inconsistent use of oral PrEP with episodes of CLI or STIs when not on PrEP.	✓	✓	
Clinical history of ceasing and/or recommencing oral PrEP due to struggles with adherence or failure to adhere.		✓	
Patient reports a strong belief that they will not be able to adhere to oral PrEP in the future.	✓	✓	✓
Patient reports wanting to cease oral PrEP despite evidence of ongoing HIV acquisition risk if PrEP is ceased.	✓		
Patient reports inability to use oral PrEP due to privacy concerns and risk of stigma/discrimination or interpersonal or state violence.	✓	✓	✓
Clinical history of ongoing side effects the clinician believes are related to oral PrEP, e.g. gastrointestinal symptoms such as nausea, diarrhoea, constipation; headaches; fatigue; other.	✓	✓	
Coverage of specific periods, such as travel or events during which adherence to oral PrEP may be difficult, or work requirements that preclude predictable oral PrEP adherence, e.g. travel to countries where male-to-male sex is criminalised, work environments such as off-shore drilling, mining, living on site at work and so on.	✓	✓	✓

Effectiveness, safety and clinical questions and outcomes

This section explores the research questions and outcomes focused on the **effectiveness, safety, and clinical characteristics** of CAB-LA as PrEP. These proposed outcomes would be measured and analysed at the level of individual patients (although comparisons across sites or clusters of sites can be explored at the analysis stage). It is possible to have multiple, "equal" effectiveness outcomes, or to prioritise them in some way (e.g. to have one primary outcome and several secondary ones). There may also be specific effectiveness outcomes/research questions that are only explored in the context of sub-studies involving a subset of all patients.

Proposed effectiveness, safety, and clinical outcomes

- Proportion of on-time injections in patients taking CAB-LA injections. (This outcome is favoured by the study team as being the primary effectiveness, safety, and clinical outcome.)
- HIV incidence, stratified by characteristics of interest such a demographics, clinic type and location, arms of the trial (if relevant), behaviours, and so on, including description of any observed breakthrough infections.
- Incidence patterns of drug resistance in patients who acquire incident HIV infection.
- STI incidence, stratified by characteristics of interest such a demographics, clinic type and location, arms of the trial (if relevant), behaviours, and so on.
- Number, proportion, and incidence of serious adverse events.
- Sexual behaviours, stratified by characteristics of interest such a demographics, clinic type and location, arms of the trial (if relevant), behaviours, and so on.
- Number, proportion, and incidence of patients continuing CAB-LA injections, ceasing CAB-LA injections, and/or switching to oral TDF/FTC PrEP.
- In patients who cease CAB-LA injections (either during or after the trial during the "tail"): adherence to PrEP or other safe sex methods and frequency of "unprotected" condomless intercourse acts.
- Number, proportion and incidence of planned and unplanned missed injections/visits, and the stated reasons for these.
- Patient factors and clinic factors associated with late CAB-LA injections.

Protocol for seroconversion

The protocol for seroconversion will be compatible with the guidance provided in the ASHM PrEP Guidelines for managing HIV infection in people who have used oral PrEP for HIV prevention.

Implementation questions and outcomes

Our formative research has outlined several complex **implementation-related issues** that could be explored in this trial. We believe that some of these issues are of high priority and should be rigorously evaluated, while there is uncertainty about others.

We intend to examine a range of "implementation outcomes" in the trial. Implementation outcomes are conceptually different from the effectiveness, safety and clinical outcomes discussed above. They include research questions relating to acceptability to patients and providers, feasibility of implementation, appropriateness of the product and protocols, how well the product was implemented at clinical sites, how it was implemented, strategies used to support implementation, and barriers and facilitators to implementation. These implementation-focused research questions can be assessed at the patient, clinician, clinic, or policy level.

Proposed implementation outcomes and measures

The implementation outcomes of the trial will largely depend on several design considerations. For example, if we run the trial as a cluster randomised trial in which some clinics are randomised to an "enhanced" package of implementation supports and others to a "routine" package, then the primary outcome would be to compare the two study arms on key measures. We will determine the specific design details in the coming months.

However, some of the key measures we are likely to include to measure implementation outcomes are summarised in Table 3.

Table 3. Implementation measures, definitions, and applicability to patients and clinic staff.

Outcome measure	Definition[129]	Patients	Clinic staff
Acceptability	Perceived satisfaction with aspects of the intervention including content, complexity, comfort, delivery, and credibility.	✓	✓
Adoption	Intention, initial decision, or action to try an innovation or proven intervention.	✓	
Feasibility	Extent to which a new intervention can be successfully used or carried out within a given setting.		✓
Appropriateness	Perceived fit, relevance, compatibility, suitability, usefulness, and/or practicability of the intervention.	✓	✓
Fidelity	Degree to which an intervention is implemented as it was prescribed in the original protocol or as it was intended by the developers.		✓
Penetration	Degree to which an intervention is integrated into the service setting and its subsystems.		✓
Cost	Cost impact of an implementation effort.	✓	✓
Modifications to strategies	Formal documentation of modifications to implementation strategies.		✓
PrEP satisfaction	How satisfied the individual is with being on PrEP and their experience of PrEP clinical service delivery.	✓	

Note: Tick mark indicates that data will be collected from the participant type.

Specific strategies to support implementation of CAB-LA

There is a large range of implementation strategies that can be evaluated, and a common implementation science trial design is to combine strategies together into an "enhanced" package of supports provided to clinics, to be compared to a "routine" package. In consultation with clinics and other stakeholders, we will need to identify, choose, and develop the specific strategies. Some potential strategies to support CAB-LA implementation could include:

- Training program for clinical staff (and potentially administrative staff) and post-training coaching from expert clinician/research team
- Specialised training in providing injections
- Specialised information materials for patients
- Audit and feedback to clinical staff
- Enhanced follow-up strategies such as a peer navigator program (e.g. in partnership with community organisations); enhanced reminder system/protocol; a mobile or web-based app; changes to the patient management system or electronic medical record; or other options
- Visit mapping process to identify potential problem points and develop systemic solutions
- Visit simplification or streamlining (e.g. doctors see patients at first and second visits, and nurses see patients for follow-up)
- Regular implementation meetings within clinics (and potentially the research team)
- Develop and implement tools for quality monitoring.

Following Proctor et al (2013), we would aim to name each specific strategy, explicitly define it, and specify/operationalise it (specify the actor, the action, the action target, the timing, the dose, the implementation outcome affected, and the justification).[130]

An important role of implementation science is to formally document and assess modifications to any implementation strategies being explored, used, and/or evaluated in the study. We propose to ensure that the study includes procedures for documenting such modifications. There are validated tools used in other implementation science studies that we can utilise, such as the *FRAME-IS* framework, which formalises the collection of data on what is modified, the nature of the modification, whether the modification threatens the fidelity and core components of the intervention, the goal of the modification, the level of the rationale for the modification, when it is modified, who participated in the decision to modify, and how widespread the modification is.[131]

Managing clinic visits and administering injections

As this is a completely new PrEP modality, it is not yet known what the optimal process for CAB-LA clinic visits will be, and this should be an important research question for our trial. The precise design and flow of clinic visits could be developed by the research team (in consultation) and mandated in the study protocol for all sites and patients, different processes could be allocated and explicitly evaluated by comparisons at the site level, or clinics could be asked to develop and implement their own processes (with the study observing and evaluating these). As with the above, documenting modifications to processes, and how these evolve over time, will be important.

A critical question for the clinic processes is who within the clinics can or should give the actual injections (e.g. doctors, nurses, nurse practitioners, trained peers). It is possible that different approaches will affect measures of feasibility, acceptability (to patients and clinics), and appropriateness. As with the clinic processes above, this question could be examined in an observational design or an allocated or randomised design. However, it will be important to take into account the distinct features, capacities and staff of each individual clinic.

HIV testing and the possibility of same-day initiation

The TGA does not require RNA testing for those using CAB-LA in Australia, but does require a documented HIV-negative test before initiating CAB-LA, "in accordance with applicable guidelines".[18] The TGA provided no timeframe for the documented HIV-negative test. Thus, an important question for implementation is how to manage HIV testing prior to CAB-LA initiation.

A key factor here is that the National PrEP Guidelines currently allow for the same-day initiation of oral TDF/FTC PrEP, and clinics have developed their own various ways of facilitating this to balance both the risks of initiating PrEP with a potential prevalent HIV infection versus the risks of delaying initiation in an individual identified as high risk for HIV.

Allowing for same-day initiation of PrEP is critical. We do not want to go "backwards" with this and reintroduce waiting periods for HIV test results. However, there does need to be recognition that injecting a long-acting agent into a patient's body comes with different risks (safety/tolerability; prevalent HIV infection and the risk of drug resistance) compared to prescribing an oral pill that can be quickly ceased and has a much shorter pharmacokinetic half-life.

Key questions include:

- How might we define the timeframe for when a previous HIV-negative test result "qualifies" as recent enough to allow CAB-LA initiation?
- Could we consider using a rapid antibody/antigen test at the time of screening, in parallel with laboratory HIV testing, and would this be feasible in clinics?
- Could patients initiate CAB-LA on the same-day, with the risks clearly explained in the informed consent process, and with a view to bringing them back in immediately if positive for discussion about immediate treatment initiation using three-drug therapy?
- Could we develop an algorithm to allow some patients to have same-day initiation (e.g. PrEP-naïve people with a negative rapid test result; people already on PrEP with good adherence and a recent HIV test)?

There are several options, and if it was believed to be an important enough issue, there is the possibility that different testing algorithms/approaches could be compared and evaluated. Another option is that we could start the trial with one standardised approach, and introduce a new approach later once the acceptability and feasibility of the initial approach has been evaluated. A further option is to mandate one standardised approach with most patients, but conduct a sub-study among a subset of patients. Again, the approach taken in the sub-study could then be implemented more broadly if found to be acceptable, feasible, and appropriate.

STI testing schedule

The Australian Sexually Transmitted Infection and HIV Testing Guidelines 2019,[132] ASHM National PrEP Guidelines 2021,[133, 134] and Australian STI Management Guidelines for Use in Primary Care[135] state that GBM should be tested for STIs every three months, including syphilis, gonorrhoea, and chlamydia. However, the injection schedule for CAB-LA is every two months.

Internationally and locally, concerns are being raised about whether we may be over-testing GBM for bacterial STIs. One argument is that the approach of high frequency screening among all sexually active GBM has not led to population-level decreases and control of STIs. (Although it could be argued that the recommended frequency in the guidelines has never been achieved at a population level.) Another argument is that high frequency screening picks up a lot of asymptomatic gonorrhoea and chlamydia in GBM who have sex with men only, in whom these infections have little negative health impact, which in turn leads to the overuse of antibiotics and has the potential to lead to population-level antimicrobial resistance.

We believe there is genuine uncertainty about whether we should test participants in our trial at every CAB-LA injection visit, and therefore, the frequency of STI testing should be a key research question in the study.

We propose that HIV and syphilis testing be conducted at every visit, but that different approaches to the testing of other STIs should be compared, e.g. STI testing at every visit (six times per year) or at every second visit (three times per year). The implementation research question would be to compare the feasibility, acceptability (to patients and clinics), and appropriateness of the STI testing protocols. Furthermore, the method would be designed to determine any disadvantages to patients, clinics, or public health if testing for gonorrhoea and chlamydia was conducted only at every second visit.

These research questions could be formally explored in multiple ways, including site-level randomisation, site-level allocation, individual-level randomisation, or allowing the sites to choose the approach most appropriate for them.

Injection window, and planned and unplanned missed injections

The injection window of seven days before and seven days after the scheduled injection time has been highlighted in our formative work as a potential challenge to clinics and to patients.

A key question is whether or not there is any real-world flexibility around this schedule and how to operationalise this in a trial protocol. That is, is seven days before the scheduled injection the *earliest* allowable? Could there be times where slightly earlier could be allowed? And if so, how much earlier (or later) could be allowable? This issue is especially relevant for people who travel frequently and who may not accept the option of oral pills to cover a planned missed injection.

In general, we believe that the protocol for planned missed injections should be guided by the registered product information approved by the TGA (i.e. patients who know they will miss an injection window will be given oral pills to cover the injection). We will need to ensure we have a

method to measure how often this happens, who it happens in, how well the patients adhere to the pills during the missed injection period, and how acceptable this approach is to patients.

Unplanned missed injections present a greater challenge. The registered product information simply states that when an unplanned missed injection occurs, the CAB-LA initiation process must start over (i.e. a confirmed negative HIV test result, one injection, another injection one month later, then injections two-monthly thereafter). But there are some complexities in dealing with missed injections themselves. For example:

- Should clinics book patients for their injections towards the beginning of the injection window, so that there is more time to fit them in over the next two weeks if the scheduled appointment is missed?
- Should clinics develop streamlined prioritisation systems to ensure a patient can get the injection whenever they present to the clinic during their scheduled window, regardless of whether they have an appointment?
- What level of follow-up of missed injections should clinics be responsible for *in the real world*? With oral PrEP, clinics typically do not keep track of their patient's supply of pills, and do not actively follow up patients if they do not return for a prescription every three months. Should CAB-LA be done the same way, or is there a greater onus on clinics to prepare for visits and follow up any missed injections? If there is, how will this be feasible?
- Could technology help? (e.g. an app, or SMS reminder systems that are linked into the electronic patient management system/electronic medical record.)
- If a patient misses their injection window entirely, what should be the precise protocol to re-initiate them on CAB-LA injections? Can there be a grace period (e.g. if they miss the window by two days) or is it essential to keep to the seven days as specified?
- Is there a role for oral CAB-LA tablets for people who have unplanned missed visits, and if so, what would this role be?

Finally, we will need to ensure we have a way to measure the effort, both at the clinic-level and patient-level, that goes into managing the tight 14-day injection window. We know from previous CAB-LA ART and PrEP trials that the vast majority (~95%) managed to have their injections within their windows – but how hard or easy was this to achieve?

Discontinuation and switching to oral PrEP

Some patients may discontinue CAB-LA injections after initiating them in the trial (either with a plan to discontinue PrEP entirely or to switch to oral TDF/FTC PrEP), and depending on post-trial access to CAB-LA, all patients may potentially face discontinuation at some point.

The Australian registered product information states that people who discontinue CAB-LA injections should "consider" other forms of PrEP and should start two months after the last injection. This is currently somewhat vague, and in the absence of further guidelines, the study will likely need to develop a single discontinuation protocol to be followed by every patient who discontinues, or perhaps develop more than one protocol and compare them.

For example, the product information does not mention other forms of safe sex that an individual might use, which may forego the need for continuation on PrEP (e.g. if they have no sex at all; if

they enter a monogamous relationship with a seroconcordant partner or an HIV-positive partner with suppressed viral load; if they consistently use condoms; or if they have casual sex with HIV-positive partners with suppressed viral load). Additionally, even if they are suitable for continuation on PrEP, patients and clinicians will need to consider what type of oral PrEP should be recommended for each individual (i.e. daily or on-demand). The risk of drug resistance is only present if an individual, during the pharmacokinetic tail period where they have non-protective levels of drug in their system, engages in "unprotected" acts of condomless intercourse where there is a reasonable risk of transmission. Depending on the circumstance of the individual, ongoing oral PrEP really may not be needed.

We will also need to acknowledge that some patients may actively choose to stop CAB-LA injections because they decide it is not suitable for their individual circumstances, and may switch to oral TDF/FTC PrEP. We will need to ensure that the trial has measures to assess this. These individuals should stay in the trial despite not having CAB-LA injection anymore, and be monitored over time.

Drug dispensing

At this early stage, it is unclear how CAB-LA dispensing will look in the real world. We may be able to learn some lessons from the rollout of long-acting Cabotegravir/Rilpivirine injections for ART; however, it should be noted that the requirements are somewhat different given that the Rilpivirine component of that product requires cold-chain transport and storage, whereas CAB-LA does not. This issue relates heavily to the questions discussed above about 1) how real-world we want this trial to be, and 2) whether CAB-LA is likely to be a specialist/niche product or something used more broadly. For example:

- Should patients be required to receive a prescription and pick the drug up themselves from a pharmacy (more real-world), or should clinics provide the drug (less real-world)?
- Should patients be required to pay for the drug (at the PBS price)?
- How will the dispensing of the oral Cabotegravir tablets be organised – again, will these be held at pharmacies or will clinics have a supply?

Designing patient and community messaging

There are some complex issues relating to CAB-LA as PrEP that will need to be explained to patients and potentially to the broader community (especially GBM). As with many of the topics in this section, this could be the focus of a specific research question (i.e. different materials developed and explicitly compared) or there could be a single set of communication materials applied consistently, co-designed with stakeholders and community. It should be acknowledged that clinicians can have a strong influence over patients, and that their own attitudes towards CAB-LA may impact their patients' attitudes. Given that we are documenting some hesitancy towards CAB-LA in our formative work, this has the potential to impact the acceptability and feasibility of CAB-LA in the trial.

Potential sub-studies

There may be some specific questions that we could explore in the context of sub-studies among a subset of patients or clinics.

Drug concentrations

There may be interest in assessing drug concentration levels in a randomised subset of patients on CAB-LA injections (i.e. bloods stored for later analysis). However, given that pharmacokinetic studies of CAB-LA have shown that on-time injections typically lead to protective levels of the drug, we would need to be clear about the purpose. Collecting and storing blood samples is expensive, so there would need to be a strong rationale.

Breakthrough infections

Similarly, there are ongoing concerns about the small number of breakthrough infections seen in *HPTN083* despite on-time injections.[13] This issue is likely to be important to the community. We may wish to conduct a sub-study of those who acquire incident infections, such as taking bloods for testing drug levels. However, a limitation will be that the drug levels in blood at the time of HIV *diagnosis* may not reflect the levels at the time of *infection*. We could design a protocol for enhanced data collection such as detailed medical record review,[136] or interviews with the patient and clinician for anyone who acquires incident HIV.

RNA testing

The TGA does not require RNA testing for those using CAB-LA in Australia.[18] However, we are still concerned about people who may acquire incident HIV when on CAB-LA and therefore may have delayed detection of the infection.[13] A potential sub-study, or simply part of the overall trial protocol, could include the selective use of RNA testing in specific individuals. These may include individuals who have symptoms consistent with seroconversion illness or who are late for their injection. It is likely beyond the capacity of this trial to collect blood for later RNA testing, as to be useful, this would need to be done on all patients in the study.

Self-injection or non-clinician administration of injections

During the clinician and end-user workshops there was positive support for studying the effectiveness of training people to self-administer CAB-LA or have a non-clinician do it for them in the home setting. In addition, the service providers participating in our co-design workshop endorsed the idea of having a telehealth or videohealth consult with a clinician who could observe

and guide them whilst they are self-administering the injection. Patient populations who might benefit from this approach include those who are living in rural and remote regions and people who for various reasons are unlikely, reluctant, or unable to attend traditional healthcare settings on a regular basis.

CAB-LA and oral PrEP switch patterns

While patterns of switching between oral PrEP and CAB-LA would be monitored in the main study, we may want some specific focus in a sub-study on preferences for and uptake of switching between CAB-LA and oral PrEP during the study. We have found in our co-design workshops that end-users are interested in using CAB-LA and switching back to on-demand PrEP to respond to periods of their life when they are having more, or less sex, respectively. Alternatively, some might only use CAB-LA for periods of higher sexual activity and then stop CAB-LA and not use oral PrEP at all when they are having less sex.

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