World Health Organization

GUIDELINES ON

LONG-ACTING INJECTABLE CABOTEGRAVIR FOR HIV PREVENTION

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ABBREVIATIONS AND ACRONYMS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
CAB	cabotegravir
CAB-LA	long-acting injectable cabotegravir
DTG	dolutegravir
DVR	dapivirine vaginal ring
FTC	emtricitabine
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
INSTI	integrase strand transfer inhibitor
ISR	injection site reaction
LMIC	low- and middle-income country
MPT	multi-purpose prevention technology
NAT	nucleic acid test
PEP	post exposure prophylaxis
PICO	population, intervention, comparator, outcome
PrEP	pre-exposure prophylaxis
RCT	randomized controlled trial
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
WHO	World Health Organization

DEFINITIONS OF KEY TERMS

Age groups

In these guidelines the following definitions for adults, adolescents, children and infants are used in recommendations for specific age groups. It is acknowledged that countries may have other definitions under national laws.

- An adult is a person older than 19 years of age.
- An adolescent is a person 10–19 years of age inclusive.
- A child is a person from one year of age to younger than 10 years of age.
- An infant is a child younger than one year of age.

Key populations

Key populations are defined as groups who, due to specific higher-risk behaviours, are at increased risk of HIV, viral hepatitis or STIs irrespective of the epidemic type or local context. Also, they often have legal and social issues related to their behaviours that increase their vulnerability to HIV. WHO defines key populations as 1) men who have sex with men; 2) people who inject drugs; 3) people in prisons and other closed settings; 4) sex workers; and 5) trans and gender diverse people. Key populations are important to the dynamics of HIV, viral hepatitis and STI transmission. They also are essential partners in an effective response to the epidemic.

Long-acting injectable cabotegravir (CAB-LA)

Long-acting injectable cabotegravir (CAB-LA) is an integrase strand-transfer inhibitor (INSTI). It is given to people who do not have HIV infection, at a dose of 600 mg, intramuscularly, four weeks apart for the first two injections and every eight weeks thereafter for the prevention of HIV acquisition.

Substantial risk

HIV acquisition risk varies considerably within populations and geographical locations. Population-level HIV incidence is an important determinant of individual-level risk of HIV acquisition. However, when considering who could benefit from pre-exposure prophylaxis (PrEP), it is important to consider the characteristics and behaviours of individuals and their partners that could lead to HIV exposure. Even in locations with a low overall HIV incidence, there may be individuals at substantial risk who could benefit from PrEP services. Individuals requesting PrEP should be given priority to be offered PrEP since requesting PrEP indicates that there is likely to be a risk of acquiring HIV. When PrEP use is risk-informed (taken during periods of risk of HIV acquisition), PrEP can be cost-effective. Cost-effectiveness will vary across countries, populations, and PrEP products. However, cost–effectiveness should not be the only consideration when implementing PrEP programmes, since remaining HIV-negative and having control over HIV risk has intangible value to people and communities.

EXECUTIVE SUMMARY

Purpose

Achieving the Global AIDS target for 2025 of ensuring that 95% of people at risk of HIV acquisition have access to HIV prevention options, requires a focus on expanding effective HIV prevention choices. Pre-exposure prophylaxis (PrEP) is a key component of combination HIV prevention. In 2015 the World Health Organization (WHO) recommended oral PrEP containing tenofovir disoproxil fumarate (TDF) for people at substantial risk of HIV *(1)* and, in 2021, recommended the dapivirine vaginal ring (DVR) for cisgender women at substantial risk of HIV *(2)*. Although expansion of access to and uptake of oral PrEP has been slow, more countries are now including oral PrEP in their national guidelines and there is increasing access and uptake, especially in sub–Saharan Africa. Although some countries have begun to include the DVR in their national guidelines, no country has yet started to provide the DVR in their national programme. Potential barriers to the uptake and effective use of oral PrEP, such as not wanting to take an oral pill regularly, may be overcome with a long-acting injectable option. This new guidance recommends offering such an option: long-acting injectable cabotegravir (CAB-LA). Offering additional PrEP choices has the potential to increase uptake and effective use of PrEP, and HIV prevention overall, as it allows people to choose a method that they prefer.

Since the release of the recommendation for the DVR, included in the WHO 2021 *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring (3)*, new evidence from two randomized controlled trials (RCTs) has emerged on the effectiveness of CAB-LA. Ministries of health, implementers and communities have asked WHO to review the evidence and provide guidance in a timely manner on this additional effective HIV PrEP option.

This guideline outlines the rationale and evidence for a new recommendation on HIV prevention. Consistent with previous WHO guidelines, this guideline is based on a public health approach that considers effectiveness, acceptability, feasibility and resource needs across a variety of settings. This guideline also highlights important considerations for effective implementation and the need for implementation science to address research gaps across a variety of geographies and populations.

Guideline development methodology

In response to the availability of new evidence on the efficacy of CAB-LA for the prevention of HIV acquisition, external experts and stakeholders proposed to make this recommendation as an addition to the HIV prevention recommendation in the 2021 *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring (3)*.

As a result, from January to May 2022, the WHO Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes led the development of new guidance with support from a Guideline Development Group (GDG) and an External Review Group. The WHO steering group formulated the population, intervention, comparator, outcome (PICO) question. External researchers, supported by WHO, conducted the systematic reviews of the evidence to answer this question. The evidence was synthesized and incorporated into an evidence-to-decision framework to help inform the discussions at a virtual GDG meeting that took place on 9 and 10 March 2022, chaired by two members of the GDG and facilitated by a methodologist. The GDG members made judgements on the potential benefits and harms of the intervention, stakeholder values and preferences, acceptability, feasibility, resource use and considerations of human rights and equity. Taken together and using the Grading of

Recommendations Assessment, Development and Evaluation (GRADE) methodology, these judgements contributed to determining the strength and direction of the recommendation. The recommendation was made by consensus.

New recommendation

> Long-acting injectable cabotegravir may be offered as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches *(conditional recommendation; moderate certainty of evidence)*.

The recommendation is in line with and builds upon existing WHO recommendations that support offering a range of effective options for HIV prevention. Using the GRADE methodology, the GDG determined the evidence to be of moderate certainty. Based on this evidence, the GDG members were unanimous in making a conditional recommendation to WHO that CAB-LA be offered as an additional HIV prevention choice.

Implications for implementation

> This guideline seeks to support countries to provide an additional HIV prevention option and, thus, increase access to and uptake of comprehensive HIV prevention approaches.

CAB-LA should be delivered as an additional choice alongside other PrEP options, including oral PrEP and the DVR, as part of a comprehensive HIV prevention approach. To date, provision of CAB-LA has largely been limited to trial settings, certain geographies and specific populations. This guideline outlines operational research to address research and implementation gaps, and to inform decisions on how to approach the implementation and scale-up of CAB-LA successfully. The GDG stressed that operational research – and implementation of services itself – must involve the full participation of interested communities from inception to implementation.

As countries plan the introduction of CAB-LA, considerations should include optimal HIV testing strategies for initiation and continuation; service delivery models including differentiated service delivery to maximize accessibility and acceptability and to integrate CAB-LA as an additional choice in comprehensive services; and activities to create awareness and demand as well as training and support of providers. Operational research is needed to evaluate CAB-LA provision for key populations, particularly sex workers, people who use drugs, trans and gender-diverse people, as well as adolescents. As PrEP is a new product, research is also needed across a range of priority areas including optimal testing strategies and impacts on drug resistance, safety in pregnancy and breastfeeding, service delivery models and population-level impacts and cost-effectiveness, to support inclusion of CAB-LA as part of differentiated service delivery for HIV prevention.

1. INTRODUCTION

1.1 Background

HIV remains a major public health issue, with approximately 37.7 [30.2–45.1] million people living with HIV and 1.5 [1.0–2.0] million new infections in 2020. Despite global commitments to reduce new infections by 75% between 2010 and 2020, to fewer than 500 000, new HIV infections declined only 31% over that decade *(4)*. Key populations[1] and their partners accounted for 65% of the new infections globally and for 93% of new infections outside sub-Saharan Africa. Adolescent girls and young women accounted for 25% of new infections in sub-Saharan Africa in 2020, despite constituting just 10% of the population. In 2021, with the new Political Declaration on HIV and AIDS *(5)*, United Nations Member States committed to reducing annual HIV infections to under 370 000 by 2025 and to ensuring that 95% of people at risk of HIV have access to HIV prevention options.

Ending HIV as an epidemic and AIDS as a public health threat requires focus on providing comprehensive combination HIV prevention at scale. This includes HIV testing, condom promotion, voluntary medical male circumcision (VMMC), harm reduction services for people who inject drugs, post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP). Cultural, social and structural factors that put people at risk of HIV and undermine the availability of and access to prevention services, such as stigma, discrimination and legal barriers, must be simultaneously addressed.

PrEP is the use of antiretroviral (ARV) drugs by people who are HIV-negative to prevent HIV infection before potential HIV exposure. To support the availability of effective HIV prevention options in low- and middle-income countries (LMICs), in 2015 the World Health Organization (WHO) recommended oral PrEP containing tenofovir disoproxil fumarate (TDF) for people at substantial risk of HIV *(1)* and, in 2021, recommended the dapivirine vaginal ring (DVR) for cisgender women at substantial risk of HIV *(2)*. Although oral PrEP and the DVR are effective when used as prescribed, and the use of oral PrEP has increased considerably since the WHO recommendation *(6)*, barriers to uptake, continuation and effective use remain. People at substantial risk of HIV have diverse sexual health needs. Providing additional PrEP options has the potential to increase uptake and effective use of PrEP, as it allows people to choose their preferred method. Research from discrete choice experiments suggests that there is often an assumed preference for long-acting and discreet HIV prevention options, particularly in the form of injectable PrEP (7-12).

Providing additional PrEP options has the potential to increase uptake and effective use of PrEP, as it allows people to choose their preferred method.

[1] WHO defines key populations as men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers and trans and gender-diverse people.

Two phase III randomized controlled trials (RCTs) found that long-acting injectable cabotegravir (CAB-LA) is highly efficacious in preventing HIV infections *(13, 14)*. In December 2021 the United States Food and Drug Administration approved CAB-LA for use in the United States of America *(15)*. There has been considerable interest from multiple countries and communities in CAB-LA as a potential additional prevention choice for people at substantial risk of HIV infection. This guideline provides an evidence-based recommendation for CAB-LA as PrEP for HIV prevention, focusing on the benefits and harms for individuals and public health systems. Important considerations for effective implementation of CAB-LA as part of combination HIV prevention are highlighted.

Box 1. A note on substantial risk of HIV acquisition

HIV acquisition risk varies considerably within populations and geographical locations. Population-level HIV incidence is an important determinant of individual-level risk of HIV acquisition. However, when considering who could benefit from PrEP, it is important to consider the characteristics and behaviours of individuals and their partners that could lead to HIV exposure. Even in locations with a low overall HIV incidence, there may be individuals at substantial risk who could benefit from PrEP services.

Individuals requesting PrEP should be given priority to be offered PrEP since requesting PrEP indicates that there is likely to be a risk of acquiring HIV. When PrEP use is risk informed (that is, taken during periods of known risk of HIV acquisition), PrEP can be cost–effective. Cost–effectiveness will vary across countries, populations and PrEP products. However, cost–effectiveness should not be the only consideration when implementing PrEP programmes since remaining HIV-negative and having control over HIV risk has intangible value to people and communities.

1.2 Objective and intended audience

This guideline is intended to provide an evidence-informed recommendation for CAB-LA as PrEP for HIV prevention to support countries in achieving national targets of reducing new HIV infections.

The primary audience for this guideline is national and subnational programme managers and policy-makers responsible for the national health sector response to HIV, particularly in LMICs, and clinicians and other health care providers, particularly those working in primary health services, including lay and community health workers, who are the first point of contact for people who could benefit from PrEP. The guidelines are also important for people at substantial risk of HIV who could benefit from PrEP, including people from key populations, and communities affected by HIV, as well as for nongovernmental and community-based organizations. This guideline can also help donors, development agencies and international organizations to plan and implement HIV prevention programmes.

1.3 Guiding principles

The following principles have informed the development of this guideline and should guide the implementation of the recommendations:

- This guideline needs to be implemented within a public health and universal health coverage framework. In addition to strengthening HIV prevention services, the guideline should be implemented with a view to strengthening broader health systems, especially primary and community-based health services.
- Implementation of the guideline needs to be accompanied by efforts to promote and protect equity and the human rights of people at substantial risk of HIV, including by ensuring that PrEP services are accessible to all populations affected by HIV in a stigma-free and non-discriminatory environment.
- PrEP services for HIV prevention should always be voluntary, and the implementation of this guideline needs to adhere to principles of informed consent. An enabling environment that removes barriers such as stigma, discrimination and criminalization and empowers communities is important for increasing access to and uptake of PrEP services, especially among members of key and other populations at increased risk for HIV infection.
- Implementation of the recommendation in this guideline should be informed by the local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost–effectiveness.
- Implementation of this guideline requires the full participation of affected communities in developing and implementing PrEP services.

2. METHODS FOR GUIDELINE DEVELOPMENT

This guideline was developed in accordance with procedures established by the WHO Guidelines Review Committee *(16)*. The recommendation in this guideline is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to reviewing evidence and formulating recommendations *(17)*. Consistent with previous WHO guidelines, this guideline is based on a public health approach that considers effectiveness, acceptability, feasibility and resource needs across a variety of settings.

All external contributors to the guidelines, including members of the Guideline Development Group (GDG) and the External Review Group, completed a WHO declaration of interests form in accordance with WHO policy for experts (Web Annex A).

The systematic review on CAB-LA for PrEP followed a research question in population, intervention, comparator, outcome (PICO) format (Web Annex B). The systematic review findings, findings from a systematic review on values and preferences (Web Annex C), additional evidence (Web Annexes D, E, F) and evidence-to-decision-making tables (Web Annex G) were prepared in accordance with the GRADE process, and they were shared in advance and presented at the GDG meetings, where an independent methodologist facilitated the discussions.

The annex summarizes the methods for developing these guidelines. All Web Annexes are available on the WHO website.

3. RATIONALE AND SUPPORTING EVIDENCE

3.1 Summary of review findings

Evidence on the safety, efficacy and effectiveness of CAB-LA was collected in a systematic review of research on CAB-LA (Web Annex B) and from additional unpublished preliminary results from modelling presented to the GDG *(18, 19)*. The systematic review included 12 eligible articles or conference abstracts reporting data from four studies. Two studies, HPTN 083 and HPTN 084, were phase IIb/III studies assessing the efficacy of CAB-LA versus daily tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) oral PrEP (herein referred to as "efficacy studies"), while two studies, ECLAIR and HPTN 077, were phase IIa studies assessing safety and dosing of CAB-LA (herein referred to as "safety studies"). All studies were multisite RCTs. Across these trials, approximately 8120 individuals were enrolled, with 4114 individuals randomized to receive active CAB-LA. HPTN 083 enrolled cisgender men who have sex with men and transgender women who have sex with men at risk for HIV across 43 sites in the United States, Latin America, Africa and Asia. In HPTN 083 approximately 12.5% of participants identified as transgender women. HPTN 084 enrolled cisgender women at-risk for HIV across seven countries in sub-Saharan Africa. ECLAIR enrolled men at low risk for HIV infection in the United States, and HPTN 077 enrolled both men and women at low risk for HIV infection in Brazil, Malawi, South Africa and the United States. No study sought to include sex workers or people who inject drugs. HPTN 077 and HPTN 084 included a few transgender men (n=6 and n=2, respectively). Participants across all studies were ages 18 years and older.

3.1.1 Reduction in HIV infection

Together, the two RCTs found that use of CAB-LA resulted in a 79% reduction in HIV risk compared with oral PrEP.

A meta-analysis of the blinded phase of the two efficacy studies found a 79% reduction in risk of HIV acquisition among study participants receiving CAB-LA when compared with participants receiving TDF/FTC as oral PrEP. Individually, HPTN 083 estimated that the use of CAB-LA resulted in a 66% relative reduction in HIV risk compared with oral PrEP, and HPTN 084 estimated an 88% relative risk reduction. Of 20 HIV infections identified in the groups randomized to CAB-LA in the two efficacy studies following the primary analysis, five were prevalent infections present at baseline, seven were infections with no recent exposure to CAB-LA (that is, the infection occurred before the first CAB injection or infection occurred following discontinuation of CAB), three were infections that occurred during the oral lead-in phase, and five were breakthrough infections (that is, infections that occurred during appropriately timed CAB-LA injections) *(13, 20)*. The two seroconversions identified in the safety studies were considered to have no recent CAB exposure since both infections occurred in the tail phase with blood levels of CAB below the quantifiable level of detection *(20, 21)*. Data from HPTN 083 for one year of follow-up following the unblinding of participants demonstrated similar efficacy results: 13 new incident HIV infections in the CAB arm and 33 in the TDF/FTC arm. Of the 13 new infections identified in the CAB-LA arm, three were breakthrough infections (two of which had occurred during the blinded phase of the study), three occurred after delayed CAB injection (defined as missed the scheduled injection for a period of 1 to 3.6 months); and seven occurred more than six months after the last CAB injection *(22)*.

Multiple studies have shown that oral PrEP is highly effective when taken as prescribed. However, many people find it difficult to take an oral daily pill consistently. This was observed in the two RCTs. In this light, it is important to note that the 79% relative reduction in HIV risk infections in the CAB-LA arms compared with TDF/FTC is likely due largely to differences in adherence. In HPTN 084 in the 36 incident infections in the TDF/FTC arm, one participant had drug concentrations consistent with partial adherence (4–6 doses per week) and 35 [98%] had levels indicating poor or non-adherence (<2 doses per week). In HPTN 083 in the 39 incident infections in the TDF/FTC group, only two occurred in cases in which the drug concentrations measured were consistent with good PrEP adherence.

The greater efficacy of CAB-LA in the RTCs is likely due largely to better adherence to the injectable CAB-LA than to the oral TDF/FTC.

Overall, adherence to TDF/FTC was lower than for injections. In HPTN 084 samples from a randomly selected cohort of 405 participant in the TDF/FTC arm revealed poor or inconsistent adherence over time, with unquantifiable concentrations in 38% of dried blood spot samples tested; only 18% of these samples had drug concentrations consistent with at least four doses per week over the preceding month. In HPTN 083 better adherence to TDF/FTC was observed. In a randomly selected cohort of 390 participants, 72% of samples had drug concentrations (measured in dried blood spots) consistent with at least four doses per week over the preceding 1–2 months. This contrasted with high overall adherence to injections. In HPTN 084, 93%, and in HPTN 083, 92% of person–years in the study were considered to have been "covered" by injectable CAB-LA/placebo – defined as injections received within two weeks after the scheduled date.

The GDG reviewed unpublished preliminary results from mathematical models for Atlanta, Montreal, South Africa and sub-Saharan Africa (Web Annexes D and E) *(23)*. In the model for Atlanta, expanding total PrEP coverage among men who have sex with men from 30% to 40% by 2027 would avert 35% to 39% of new HIV infections among men who have sex with men over 20 years, and switching all PrEP users from oral PrEP to CAB-LA would avert up to an additional 3% of infections. In the model for Montreal, large numbers of PrEP users who were men who have sex with men would be needed for a similar impact, since, currently, PrEP coverage and HIV incidence are low in Montreal. In South Africa one model suggested that expansion of PrEP coverage from the current level of less than 1% to 13% by 2027 would avert 13% of new HIV infections over 20 years with oral PrEP alone and 17% of infections with a complete switch to CAB-LA. Another model for South Africa suggested that this effect could be roughly doubled if PrEP use is targeted during periods of substantial risk. Finally, a model of populations representing sub-Saharan Africa found that a rapid scale-up of PrEP and near-complete switch to CAB-LA would reduce HIV incidence overall from about 0.4 per 100 person-years to 0.3 in 2032 *(23)*.

3.1.2 Safety

Across the two efficacy studies, most participants experienced at least one adverse event of grade 2 or higher during the study, but no significant differences were identified in rates of any adverse events between those randomized to CAB-LA and those randomized to TDF/FTC. Similarly, across the two safety studies, there was no significant difference in the rate of any adverse event of grade 2 or higher between the CAB-LA arms and the TDF/FTC arms *(20, 21)*. In the ECLAIR study, reported

The greater efficacy of CAB-LA in the RTCs is likely due largely to better adherence to the injectable CAB-LA than to the oral TDF/FTC.

adverse events were significantly higher among participants receiving CAB-LA than a placebo *(21)*. Of note, the CAB-LA dosage in ECLAIR was 800 mg per injection, and in HPTN 077 the dosage was either 800 mg or 600 mg per injection *(20, 21)*. For both HPTN 083 and HPTN 084, the dosage was 600 mg per injection.

In HPTN 083 and HPTN 084, 5.3% and 2% of participants, respectively, reported serious adverse events, with percentages similar in the CAB-LA and TDF/FTC groups. In the safety studies, serious adverse events were reported in 5% or less of study participants across arms, with no significant difference between those receiving CAB-LA and those receiving placebo.

Adverse events stemming from injection site reactions (ISR) were reported across all studies. In HPTN 083, 81.5% of participants randomized to CAB-LA who received at least one injection reported at least one ISR. Of these, 2.4% (n=50) of participants permanently discontinued injections due to ISRs. Within the group randomized to TDF/FTC (and placebo injections), 31.3% experienced ISRs. In HPTN 084, 21% of participants experienced any ISR (32% in the CAB-LA arm versus 9% in the TDF/FTC arm). Most reported ISRs were mild, and event rates for ISRs decreased over the course of the study. There were no reported discontinuations in HPTN 084 due to ISRs. In HPTN 077, 38% of participants randomized to CAB-LA experienced an ISR, compared with 2% in the placebo group. In ECLAIR 93% of participants in the CAB-LA arm reported ISRs compared with 57% of participants in the placebo arm. Injection intolerability, which was not directly categorized as withdrawal due to ISRs, led 4% of participants in the CAB-LA arm to discontinue injections and withdraw from the study.

In HPTN 083 annualized increases in body weight were noted across study arms, with those in the CAB-LA arm gaining on average 1.23 kg per year and those in the TDF/FTC arm gaining on average 0.37 kg. In HPTN 084 investigators noted an initial, immediate weight gain among participants randomized to CAB-LA but no difference in weight increase when comparing mean increases in body weight among those in the CAB-LA arm and those in the TDF/FTC arm. HPTN 077 found no difference between study arms in weight changes or fasting metabolic parameters.

3.1.3 Drug resistance

Resistance to integrase strand transfer inhibitors (INSTI) was analysed across all included studies among participants who seroconverted during the study or who were found to have had HIV infection at baseline (Web Annex B). Of the 20 infections identified in the CAB-LA arms across HPTN 083 and HPTN 084, INSTI resistance mutations were found in seven cases (all in HPTN 083) compared with none in the TDF/FTC arm. There were no documented cases of INSTI resistance that occurred following no recent CAB exposure. In two cases INSTI resistance was acquired; it is unclear whether resistance was acquired in the other cases *(24)*. Phenotyping results, available in three cases with INSTI resistance, found varying susceptibility to commonly used integrase inhibitors; two of the three cases were resistant to CAB.

The GDG reviewed a systematic review that sought to estimate the prevalence of CAB resistance and dolutegravir (DTG) cross-resistance in persons diagnosed with HIV while exposed to CAB-LA *(18)*. Based on the Stanford University HIV Drug Resistance Database *(25)*, all seven cases of INSTI resistance conferred some level of predicted cross-resistance to DTG, resulting in a pooled prevalence of predicted DTG resistance across HPTN 083 and 084 of 22.3%. This was comparable to the prevalence of predicted DTG resistance in people failing CAB-based treatment (32.5%, across five studies) and to the prevalence of predicted DTG resistance (33.3%) from a CAB-LA pre-clinical study involving macaques.

The GDG also reviewed preliminary results from a mathematical model of rapid scale-up of PrEP and nearly complete switch to CAB-LA in sub-Saharan Africa (Web Annex E) *(19)*. The model results suggested that CAB-LA would result in a 27% reduction in HIV incidence and

reductions in the number of people living with HIV but an increase in the absolute number of people living with INSTI-resistant HIV. Around 7% of ART initiators were predicted to have INSTI resistance by 2030 (compared with 0.5% in the absence of CAB-LA). Despite the increase in INSTI resistance, CAB-LA was predicted to lead to a decrease in HIV-related mortality *(26)*.

3.1.4 Hormonal contraceptive efficacy, pregnancy incidence and pregnancy-related outcomes

A secondary analysis from HPTN 084 found that women on oral contraceptives had a lower peak CAB concentration than women not on hormonal contraception, but this did not affect any other pharmacokinetic parameters *(27)*. There were also no differences across pharmacokinetic parameters when hormonal contraception was evaluated in aggregate across types. This analysis did not consider the potential impact of CAB-LA on hormonal contraception.

No study reported on outcomes related to drug–drug interactions of gender-affirming hormone therapy and CAB-LA.

Two studies, HPTN 077 and HPTN 084, included women. In both studies pregnant and breastfeeding women were excluded from participation. Women were required to use a long-acting reversible contraceptive method throughout trial participation; thus, data on CAB-LA's impact on hormonal contraception efficacy, pregnancy incidence and pregnancy-related outcomes are limited. In HPTN 077 one pregnancy was identified in a woman randomized to CAB-LA. This pregnancy occurred in the tail phase and resulted in a live birth at 38 weeks with no birth defects. In HPTN 084, 49 confirmed pregnancies occurred (29 in the CAB arm; 20 in the TDF/FTC arm) among 48 participants. Women randomized to CAB-LA experienced more pregnancy-related events than women randomized to TDF/FTC, although no adverse events were considered product-related. No congenital abnormalities were observed. The terminal phase half-life of CAB-LA appeared similar in pregnant and non-pregnant women.

3.1.5 Behavioural outcomes, including incidence of curable STIs

No studies reported on outcomes relevant to sexual behaviour, including condom use or number of sexual partners. Neither efficacy study reported differences in incident sexually transmitted infections (STIs) between study arms.

3.2 Cost–effectiveness

Evidence on cost–effectiveness of CAB-LA was derived from a systematic review (Web Annex B) and additional modelling evidence presented to the GDG (Web Annexes D and E) *(18, 19)*. The review identified seven studies that assessed the cost or cost–effectiveness of CAB-LA or long-acting PrEP more generally. Of these, six modelled data and scenarios specific to South Africa *(28-33)*, while one study assessed costs for men who have sex with men and transgender women in the United States *(34)*.

Results of the costing studies were mixed. Several studies found CAB-LA or injectable PrEP generally could be cost-effective or cost-saving when prioritized among certain populations, particularly women *(33)*, and/or in certain circumstances where injectable PrEP could be leveraged with complementary products (for example, contraceptives and

Published literature suggests that CAB-LA or injectable PrEP could be cost-effective or cost-saving when prioritized among certain populations, particularly women, and/or offered along with complementary products.

multi-purpose prevention technologies (MPTs) *(29)*. Others found that CAB-LA or injectable PrEP generally were less likely to achieve cost–effectiveness in other circumstances, such as in a scenario involving heterosexual men in South Africa *(32)*. One study focused on the role of long-acting PrEP as a component of MPTs that could prevent pregnancy as well as HIV *(29)*. Another study focused on the cost–effectiveness of pairing injectable PrEP with injectable contraception *(31)*. Important drivers of cost included the annualized cost of long-acting PrEP and the availability of other effective HIV prevention options, as well as service delivery and uptake and availability of HIV treatment *(28)*.

The GDG also reviewed preliminary results of five unpublished mathematical models of cost–effectiveness (Web Annex D and E) *(23)*. In a high-income setting, the model for Atlanta suggested that CAB-LA could be more cost-effective than branded oral PrEP but unlikely to be more cost-effective than generic oral PrEP. In Montreal CAB-LA was found unlikely to be cost-effective. For South Africa, one model found that CAB-LA could be cost-effective if provided mainly during periods of substantial risk and priced within twice the price of oral PrEP.

3.3 Values and preferences

Evidence on acceptability, values and preferences for CAB-LA was derived from a systematic review of publications on injectable PrEP (Web Annex C), results of qualitative research from four global key population networks and a study on the perspectives of PrEP providers (Web Annex F).

Studies of potential users' values and preferences show that injectable PrEP presents an opportunity to address adherence-related challenges of oral PrEP.

A systematic review identified 99 articles meeting inclusion criteria for the values and preferences analysis (Web Annex C). Most studies were observational, cross-sectional and qualitative in North America, and men who have sex with men were the most researched respondent group. Most studies examined injectable PrEP generally, including hypothetical injectables or placebo products; six studies examined CAB-LA specifically. The review found that there was overall interest in and some preferences for injectable PrEP, although there was notable variation within and across groups and regions. The findings show that injectable PrEP presents an opportunity to address adherence-related challenges associated with daily or event-driven dosing required for oral PrEP and may be a better lifestyle fit for individuals seeking privacy, discretion and infrequent dosing. However, potential users reported concerns related to fear of needles, injection site pain and location, logistical challenges with regularly attending appointments and concerns about waning or incomplete protection.

A global online survey (n = 1353 surveys submitted and n=849 fully completed) and in-depth interviews (n=30) among PrEP providers across all regions found generally high levels of support for the addition of CAB-LA as PrEP (Web Annex F). In the survey 48% reported that they had heard of CAB-LA, and 71% would consider providing it if and when it receives regulatory approval. In the view of the interviewed providers, the main benefits include reduced adherence burden for clients and the long-acting protective effect, privacy, and the enthusiasm expressed by clients, which likely supports uptake and continuation. Primary concerns raised by providers include costs and additional workload, HIV testing requirements and drug resistance, how to safely stop CAB-LA, weak commodity management in some settings and the (re-)medicalization of PrEP.

3.4 Feasibility

Both HPTN 083 and HPTN 084 implemented CAB-LA for PrEP in a range of countries for adult cisgender men and transgender women who have sex with men and for cisgender women at risk of HIV. No studies have demonstrated the feasibility of this intervention in individuals under the age of 18 years, although studies are ongoing. The RCTs have continued as unblinded, open-label extensions, but no study or project has implemented CAB-LA for PrEP outside of a clinical trial setting.

Services for oral PrEP have been demonstrated to be feasible for all populations across regions, although, for some populations, barriers exist to accessing health facility-based services (for example, stigma, discrimination and criminalization) *(6)*.

Other injectable interventions, such as long-acting injectable contraceptives, have been implemented in various populations, particularly for cisgender women in sub-Saharan Africa *(35)*. There has been no implementation of CAB-LA outside of well-resourced and well-staffed trial settings, however, thus, limiting understanding of feasibility outside of research sites. There has also been no implementation in some population groups who might benefit from CAB-LA, including sex workers, people who inject drugs, people in prisons and transgender men (although a small number of transgender men were included in HPTN 083). This gap signals the need to explore the feasibility of incorporating CAB-LA into HIV prevention services for people from these population groups.

3.5 Equity

HIV prevention among PrEP users will contribute to equitable health outcomes by sustaining their health and the health of their sexual partners. Access to PrEP also provides opportunities for access to sexual and reproductive health services addressing multiple health needs. Considering the evidence reviewed and its discussions, the GDG noted that offering CAB-LA as an additional PrEP option could increase equity by reaching more individuals who could benefit from PrEP and who would prefer injectable PrEP over other options. However, the GDG noted that inequality in health outcomes could be exacerbated globally through differences in access to CAB-LA between and within countries.

3.6 Rationale for recommendation

Recommendation

Long-acting injectable cabotegravir may be offered as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches *(conditional recommendation; moderate certainty of evidence)*.

The GDG agreed that CAB-LA for PrEP could have substantial benefits, a judgment based on evidence of moderate certainty, as well as on acceptability to stakeholders, feasibility of implementation, potential for cost–effectiveness and potential to improved equity. The GDG considered the evidence synthesised across the domains described above where there was uncertainty and variability and made a conditional recommendation that CAB-LA may be offered as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches. The strength of the recommendation and the certainty of evidence were determined through the GRADE approach *(17)*.

The conditionality of the recommendation was also based on the acknowledgement that data were lacking on "real world" implementation, as there has been no implementation beyond the two randomized controlled trials and some short-term follow-up in their unblinded phases, and no research has involved certain key populations, including people who inject drugs, sex workers and transgender men.

There remains uncertainty around the possible harms of drug resistance and the optimal HIV testing strategy, which will greatly influence resource requirements. Resources and costs are largely uncertain and will vary greatly, but overall, they are likely to be substantially larger than for oral PrEP, particularly in the short term. Evidence on use in certain populations, including during pregnancy and breastfeeding, is lacking. The GDG noted that CAB-LA also has the undesirable potential to shift PrEP services away from the differentiated and de-medicalized service delivery models that are becoming more common for oral PrEP.

Among end-users, there is interest in injectables for PrEP, and CAB-LA could be a good choice for people who value discretion, are familiar and comfortable with needles and/or have difficulty storing or taking oral PrEP. Preferences vary across populations and regions, and there is limited experience with the actual intervention (as opposed to hypothetical preference). The GDG noted that the additional PrEP option could expand access to HIV prevention, but costs could be a barrier to equitable access.

CAB-LA could be a good choice for people who value discretion, are familiar and comfortable with needles and/or have difficulty storing or taking oral PrEP.

4. IMPLEMENTATION CONSIDERATIONS

4.1 HIV testing and other testing requirements

As with oral PrEP and the DVR, HIV testing is required before offering CAB-LA and should also be done before each injection while using CAB-LA and, ideally, regularly after CAB-LA discontinuation. HIV testing can be conducted according to the WHO testing strategy for HIV diagnosis in people >18 months of age, using the national testing algorithm composed of quality-assured serology assays (that is, rapid diagnostic tests and enzyme immunoassays).

Only individuals who are HIV-negative should be initiated on PrEP. Individuals with one or more reactive test results prior to initiating CAB-LA or while taking CAB-LA need further testing to confirm their HIV diagnosis. Anyone with inconclusive results should be referred to return for further testing to confirm HIV status after 14 days. Brief messages, support and linkage to ART should be provided for anyone with a confirmed HIV diagnosis.

4.1.1 Delayed immune response

While people rarely present during acute HIV infection, initiation of PrEP during this period can contribute to a delayed immune response to HIV. This includes a dampening of virus, so viral components such as RNA may not be detectable, and this in turn will result in a delay in the generation and appearance of anti-HIV antibodies. If CAB-LA is initiated or continues to be used after HIV infection, delayed diagnosis and, thus, linkage to ART are likely. Furthermore, the risk of HIV drug resistance may increase. Similarly, after completion or discontinuation of injections with CAB-LA, diagnosis may be delayed when individuals acquire HIV, leading to a potential risk of HIV drug resistance. CAB-LA drug concentrations decline slowly over time, resulting in a pharmacokinetic "tail" (HPTN 077 reported that the median times to the lower limits of quantification were 44 weeks for cisgender men and 67 weeks for cisgender women). Although a rare occurrence, HIV drug resistance emerging after CAB-LA exposure could compromise the effectiveness of INSTI drugs widely used for HIV treatment, notably DTG. More evidence is required to better quantify and understand this.

4.1.2 Nucleic acid testing

Some programmes may also offer nucleic acid technologies (NAT) testing, in addition to the national algorithm, at initiation or to those taking CAB-LA. NAT may detect HIV earlier than serology assays, especially prior to the presence of ARVs, and, thus, possibly reduce the development of drug-resistance. WHO currently does not recommend the use of NAT for HIV diagnosis of adults, and most NATs do not have regulatory approval for HIV diagnosis in adults. NAT alone is not a diagnostic test for people >18 months and cannot rule out HIV infection. Also, NAT can contribute to an increased number of discrepant results, and more costly testing algorithms need to be used to resolve discrepancies. NAT is not widely available in low- and middle-income countries, and high costs and lengthy turnaround times can limit its usefulness. According to a recent systematic review, the time between laboratory-based NAT sample collection and delivery of results was a median of 35 days *(36)*.

The potential public health benefit of including NAT as part of testing strategies and algorithms for CAB-LA initiation and/or monitoring remains uncertain. Programmes need to carefully consider the public health impact when selecting their HIV testing strategy and approaches. This will include adapting HIV testing to the way CAB-LA will be delivered and the priority populations that are being served. Weighing the trade-offs will be important to ensure that HIV testing approaches do not hinder or discourage users from accessing CAB-LA. In addition to the necessary regulatory approvals and adequate resources, where national programmes decide to use NAT before or during use of CAB-LA, a clear plan for diagnosing HIV when test results conflict and a strategy for results reporting are required (for example, when an NAT detects HIV while a serology assay is non-reactive).

Key messages on HIV testing for CAB-LA

- It is important for programmes to select a testing strategy and algorithm that promotes access to CAB-LA among those who would benefit most.
- Programmes can employ the current national HIV testing strategy and algorithm, using a combination of RDTs and enzyme immunoassays according to WHO recommendations.
- Some countries and programmes may include NAT where feasible, in addition to the national algorithm, particularly at initiation, prior to the presence of ARVs. Where NAT is implemented, it is important to have the necessary assays, resources, regulatory approvals and a clear testing strategy for resolving discrepant results and establishing HIV infection before initiating life-long ART.
- Countries need to consider the feasibility of using NAT before CAB-LA initiation, and while taking CAB-LA. While NAT before CAB-LA initiation, and while taking CAB-LA, might prevent a small number of cases of drug resistance, countries need to consider the feasibility of NAT. There are also uncertainties as to what impact these mutations will have on subsequent ART.
- Ongoing monitoring of implementation is needed to further optimize HIV testing approaches for CAB-LA.

4.1.3 Hepatotoxicity

Hepatotoxicity (as indicated by raised liver function levels) has been reported in a small number of people receiving CAB-LA *(37)*, although similar levels were found among those receiving placebo injections in CAB-LA trials. Liver function testing (such as measuring alanine transaminase) can be considered before and during CAB-LA use. CAB-LA should not be initiated in people with advanced liver disease or acute viral hepatitis and should be discontinued if hepatoxicity is confirmed. CAB-LA injections should not be delayed while waiting for results of liver function tests, however.

4.1.4 Hepatitis

To date, clinical trial data on and implementation experience with CAB-LA among people with HBV or HCV infection are very limited. Testing for HBV and HCV and further assessment for those with reactive test results are strongly encouraged. CAB-LA may be inappropriate for those requiring treatment for HBV. More research is needed on implementation of CAB-LA for people with HBV or HCV.

If a hepatitis B surface antigen (HBsAg) test is reactive, which indicates chronic HBV infection, needs for HIV prevention and HBV treatment should be evaluated on a case-by-case basis, and PrEP and HBV treatment providers should (where possible) jointly manage these cases. CAB-LA is not active against HBV. For people eligible for HBV treatment as per WHO guidance, TDF-based oral PrEP should be offered as the preferred PrEP option. Even where there is no indication for treatment for HBV, TDF-based oral PrEP should be strongly considered, as it will both suppress HBV and prevent HIV.

If a hepatitis C (HCV) serology test is reactive and chronic infection has been confirmed, HCV treatment should be offered as per WHO guidelines, and PrEP and HCV treatment providers should (where possible) jointly manage these cases. CAB-LA is not active against HCV. There are no known drug–drug interactions between CAB-LA and treatment drugs for HCV, but data are scarce. Alternative PrEP and HIV prevention options should be considered.

As no kidney toxicity is anticipated during use of CAB-LA, kidney function testing and monitoring are not required for CAB-LA use.

4.2 Service delivery

CAB-LA provision to date has been limited to the two RCTs, with some further experience emerging from the unblinded open-label extensions of the RCTs. Services for oral PrEP, however, have been implemented in a range of settings in many countries. These include primary health care clinics, sexual and reproductive health services, ante- and post-natal care services and in community settings through, for example, key population-led clinics and mobile clinics. Many of these settings have experience in implementing other types of preventative health services relevant to the provision of CAB-LA.

PrEP services provide an opportunity to offer a comprehensive package of services tailored to the needs of the individual and local context, including testing and treatment for STIs and viral hepatitis, although receiving PrEP should not be dependent on receiving additional services.

Service delivery models should be adapted to local context and community preferences. It will be critical to engage with people who could benefit from PrEP and service providers when designing services for CAB-LA. Experience with oral PrEP suggests that services should be provided in a range of settings, including in communities, to meet preferences of people who could benefit from PrEP, overcome barriers to access and improve uptake and continuation of PrEP use. Also, services should aim to align clinic visits for PrEP with complementary services such as contraceptive services and gender-affirming services for trans and gender-diverse people. Services can explore options for differentiated service delivery packages in order to minimize the burden on clients, providers and health systems.

Special consideration will be needed to make sure that CAB-LA services for members of key populations and young people are acceptable and safe for them.

Members of key populations and adolescents and young people typically experience the greatest challenges to accessing PrEP services. These challenges include stigmatization, discrimination and criminalization. Adolescents may face additional age-related legal, policy, regulatory and social barriers to accessing health and HIV prevention services, including age of consent laws that limit access to HIV testing and prevention services and challenges with logistics and expenses for attending services. As a result, special consideration will be needed for acceptable and safe approaches to deliver CAB-LA to members of key populations and to young people. This should include attention to the needs and priorities of key populations and young people and should ensure that they are meaningfully involved and consulted.

4.3 Comprehensive services

PrEP, including CAB-LA, should be provided in combination with other effective and well-established prevention approaches and health services. Depending on the local context and the needs and preferences of the populations that could benefit from PrEP, this may include the provision of condoms, post-exposure prophylaxis (PEP) for HIV, testing and treatment of STIs and viral hepatitis, sexual and reproductive health services, mental health support, services that prevent and protect against gender-based violence, gender-affirming care and harm reduction services for people who use drugs (including for chemsex). Where feasible, providing voluntary partner services should also be considered.

4.4 Offering a choice of PrEP options

People who could benefit from PrEP have diverse HIV prevention needs and preferences, and these may change over time. A range of PrEP options should be available to provide choice to people who could benefit from PrEP, including TDF-based oral PrEP, the DVR and CAB-LA. People interested in PrEP should be provided information on the available options and their relative efficacy and safety and counselled to make an informed decision regarding the best option for them.

4.5 Involving communities

Meeting the needs of populations at substantial risk of HIV infection and providing PrEP services, including CAB-LA, requires the full participation of communities in developing and implementing programmes. The following are good participatory practices that apply to services for all key populations:

- Recognize the leadership and resilience of priority and key populations in addressing the HIV epidemic at both the local and global levels and sustain their participation through adequate funding and support for community-led organizations.
- Strengthen the capacity of community-based organizations to educate and train their communities about all PrEP options and the importance of early treatment.
- Promote and expand community-based services, especially services led by members of priority and key populations.
- Ensure that any PrEP option is offered as a choice, free of coercion and with access to other prevention strategies that individuals at substantial risk may prefer.
- Increase political commitment to rights, including the rights of priority and key populations, by decriminalizing consensual sexual activity, gender expression, sex work and drug use.

4.6 Creating awareness and demand

As CAB-LA is a new PrEP product, many communities and providers have limited or no awareness of it. Countries wanting to introduce CAB-LA as an additional HIV prevention option should conduct an awareness programme for communities and providers before and during introduction as a first step towards creating demand and enabling people to make informed choices. Engagement with networks of individuals who could benefit from PrEP and with community organizations, including key populations networks, is needed to understand concerns and respond to questions about this new product. Community acceptance is critical to ensure that CAB-LA can be provided in an acceptable and stigma-free way, which supports uptake and effective use of any PrEP product.

4.7 Adherence support and discontinuation

PrEP products, including CAB-LA, should be used during periods of substantial HIV risk and may be stopped if an individual is no longer at risk or decides to use an alternative PrEP product or HIV prevention strategy. The two RCTs on CAB-LA found CAB-LA highly effective at preventing HIV when CAB-LA was administered on time, although a few cases of HIV acquisition, despite on-time injections, were observed. Several HIV infections occurred when injections were delayed and after discontinuation. When a person misses a scheduled injection or discontinues PrEP, CAB concentrations in the body slowly decline. During this pharmacokinetic tail, CAB concentrations become gradually less protective against HIV acquisition, and HIV infections may occur, as observed in the RCTs. Furthermore, there is a risk of drug resistance when individuals acquire HIV soon after discontinuation, as there is when individuals acquire HIV during CAB-LA use.

It is critical to counsel clients on the need to receive injections on schedule to assure that CAB-LA is most effective, on the risks for drug resistance and on the importance of using other prevention options (such as condoms, PEP and other PrEP products) if CAB-LA is discontinued and the client remains at risk of HIV acquisition. Clients may benefit from tailored interventions to support adherence to the injection schedule, especially when receiving a new product and for certain populations, such as younger PrEP users. Support groups for PrEP users, including social media groups, may be helpful for peer-to-peer sharing of experiences and challenges.

While CAB-LA is generally safe, side effects have been observed among people receiving CAB-LA. Injection site reactions (particularly pain and tenderness) have been commonly reported among people who received CAB-LA. Other side effects reported include headache, diarrhoea, nausea and fatigue. Clients should be counselled on the occurrence of possible side effects and informed that they do not indicate a more serious underlying condition.

4.8 Training and support for providers

As CAB-LA is a new PrEP product, few PrEP providers will have experience delivering CAB-LA. However, there is extensive experience with delivering oral PrEP. National programmes should provide training and support to a range of providers in services that may be able to offer CAB-LA to clients. Training for providers will include capacity building on discussing HIV prevention needs and preferences with clients; assessing the appropriateness of the different HIV prevention options available, including CAB-LA, the DVR and oral PrEP regimens; correct administration of CAB-LA; support for safe and effective use; and provision of or referral to other services.

Providers should be trained to provide respectful, non-judgemental and inclusive services, to discuss sensitive behaviour and to build a strong patient–provider relationship. This includes training on how to have respectful and sensitive discussions with clients on HIV prevention needs and preferences and how to provide impartial expert advice on the range of PrEP and prevention options.

Service providers should be aware of the emotional and physical trauma that people at substantial risk of acquiring HIV infection may have experienced. Service providers should consider all health, social and emotional needs of people interested in and using PrEP and provide or refer to appropriate services as needed. With more widespread implementation of CAB-LA, there will be more experience on the specific training needs of different cadres of health care providers and better understanding of provider issues and concerns.

5. RESEARCH GAPS AND NEEDS

Operational research is needed to inform decisions on the implementation and scale-up of CAB-LA. It is important to partner with communities of populations affected by HIV to identify priorities and to inform the design and implementation of research and the monitoring of outcomes.

5.1 Providing CAB-LA for key populations

HPTN 083 and HPTN 084 provided PrEP to cisgender men who have sex with men, transgender women (approximately 2.5% of participants) and cisgender women. However, the studies included few transgender men and did not specify including non-binary individuals. Further research is required to evaluate CAB-LA service delivery for trans and gender-diverse people and their specific needs and preferences.

The trials on CAB-LA have not reported on interactions between gender-affirming hormones and CAB-LA. Although interactions are not expected theoretically, this is an area where further research is needed. Operational research is also needed on how to integrate CAB-LA with gender-affirming care services. Moreover, research is required on alternative injection sites for individuals with buttock implants and fillers.

None of the studies included people who use drugs nor was conducted in services for sex workers. Implementation studies are also needed to evaluate CAB-LA service delivery for these populations. For people who inject drugs, it is unclear whether CAB-LA is efficacious at preventing parenteral HIV acquisition, although people who use drugs will benefit from CAB-LA for sexual exposure.

The systematic review on values and preferences, as well as the values and preference reviews by key population groups, found that there was interest in and a preference for injectable PrEP among key populations. However, there was heterogeneity within population groups and among regions. Because most studies to date have examined people's hypothetical preferences, more research will be needed to understand the views and choices of key populations in real-world settings once CAB-LA is available to them. Moreover, where CAB-LA is found to be an acceptable and preferred option, more operational research on providing CAB-LA services for all key populations will be needed, including in the context of ongoing stigmatization, discrimination and criminalization of key populations in many countries. To support implementation and avoid exacerbating disparities, barriers and facilitators to CAB-LA access and uptake among key populations should be monitored and addressed.

5.2 CAB-LA for adolescents under age 18

Individuals under age 18 were not included in ECLAIR, HPTN 077, HPTN 083 or HPTN 084, although sizable numbers of study participants were under the age of 30. Small numbers of adolescents have been included in ongoing sub-studies for HPTN 083 *(38)* and 084 *(39)*. Additional studies including adolescent and young people are planned. These will contribute evidence on CAB-LA safety and acceptability among adolescent men who have sex with men, adolescent women, transgender women and gender-nonconforming people.

Young people frequently face additional barriers to accessing and effectively using other PrEP products, including oral PrEP, and so may require additional support for use of an injectable PrEP. Operational research with adolescent girls, young women and young members of

key populations is needed to understand the acceptability of CAB-LA as an HIV prevention option and to inform acceptable and effective service delivery approaches to support uptake, engagement with services and adherence to the injection schedule.

5.3 Safety in pregnancy and breastfeeding

In some settings pregnancy and the postpartum period are characterized by increased risk of acquiring HIV. HIV acquired during pregnancy or breastfeeding is associated with a risk of HIV transmission to the infant. It is important that women of reproductive potential do not face barriers to uptake of effective HIV prevention options such as CAB-LA.

All women enrolled in HPTN 084 and HPTN 077 were required to use a long-acting reversible contraceptive. In HPTN 084 women who were pregnant, breastfeeding or wished to become pregnant were excluded from enrolment. However, in the open-label extension amendment to HPTN 084, the requirement for all women in the trial to use contraception was removed. Women in this phase of the trial who become pregnant will now be offered the opportunity to continue CAB LA during pregnancy and breastfeeding under close monitoring.

While the very limited data available from the small number of women who became pregnant during the studies suggest that CAB-LA may be safe during pregnancy and breastfeeding, more research and safety surveillance in pregnancy are needed to monitor adverse pregnancy and infant outcomes, particularly rare adverse events, through the surveillance of PrEP within larger surveillance programmes or ARV pregnancy registries.

Antenatal and postnatal care services offer an opportunity to offer PrEP services, including CAB-LA, for women at substantial risk of HIV infection, but more operational experience and research are needed to understand the unique needs and challenges of this population and how to best address them. Contraceptive services and links to antenatal care should be available through CAB-LA services.

5.4 Optimal HIV testing strategies and drug resistance

As noted in section 4.1, the optimal HIV testing strategies, testing frequency and general approaches throughout CAB-LA implementation remain uncertain and constitute a critical research gap. Some key issues include (1) risk of delayed HIV diagnosis and treatment, (2) implications for HIV drug resistance, (3) optimal strategies for establishing HIV infection post-CAB-LA initiation and (4) feasibility and acceptability of HIV testing approaches and frequency in real- world implementation.

5.4.1 Delayed diagnosis, drug resistance and impact on treatment

There are risks of delayed diagnosis and HIV drug resistance when initiating someone already infected with HIV infection on CAB-LA, when a person acquires HIV while using CAB-LA or after discontinuation. Optimal testing frequency, alternative testing strategies (other than the WHO testing strategy for HIV diagnosis in adults) and alternative testing algorithms (using assay formats other than serology assays) have not been widely studied outside of RCTs, in routine programmatic use. The primary possible advantage of using the more expensive and complex NAT testing during CAB-LA implementation would be to reduce the development of drug resistance by diagnosing and treating people with HIV infection earlier. Across HPTN 083 and 084, the number of people who started CAB-LA with acute infection or acquired HIV while taking CAB-LA was small. Moreover, although some had drug resistance mutations, it is not known how many of these would have precluded initiation with first-line ART. In the limited data currently available on individuals who acquired HIV after discontinuation of

CAB-LA in the trials, no cases of acquired INSTI drug resistance have been reported during the tail. Further operational research and review of monitoring and evaluation data from PrEP programmes will be required to understand the risks of HIV drug resistance after CAB-LA exposure, factors potentially associated with risk of HIV drug resistance and possible impact on the efficacy of first-line recommended ART. Furthermore, it is important that future research include surveillance of pre-treatment integrase resistance and that efforts are made to optimize monitoring for drug resistance. This can include adding PrEP to WHO drug resistance surveys and efforts to establish routine sample collection, testing and sequencing for all who seroconvert while using PrEP, including those who use CAB-LA as PrEP.

5.4.2 Feasibility and acceptability

Assays for detection of acute HIV infection (that is, before antibodies can be detected), such as HIV-antigen immunoassays, fourth-generation HIV antigen–antibody immunoassays and NAT, that can be used at or near the point of care are not widely available in sites that would offer CAB-LA in LMICs. Evidence for the clinical and public health utility of these assays/testing algorithms is limited compared with that of using the national validated testing algorithms, usually RDTs. For oral PrEP, same-day initiation has been important to improve access and uptake. Use of NAT, which may require referral to another location or laboratory, sample transportation, processing time and delivery of results before initiation, is likely to prevent same-day initiation of CAB-LA. Implementation research, weighing relative harms and benefits, is needed to assess testing strategies, including testing frequency and assay format, in light of intended use.

Several other concerns about HIV testing require further research. The potential role of HIV self-testing also needs to be further explored, particularly for optimizing testing frequency and for follow-up after discontinuation. Research is needed to understand factors underlying breakthrough infections in the presence of usually protective drug levels. Such research may pave the way for additional strategies. Moreover, as few cases of INSTI resistance were identified among people exposed to CAB-LA, further research is required to determine levels and patterns of cross-resistance between CAB and DTG.

5.5 Service delivery models

Oral PrEP has been delivered through a range of services, including services for STIs and sexual and reproductive health, antenatal and postnatal care and primary health care, and in a range of settings, including clinics, pharmacies and the community. Task sharing among a range of health care providers, such as nurses and trained lay providers, is playing an increasingly prominent role in the delivery of PrEP. This differentiated PrEP delivery supports comprehensive, person-centred services, adapting them to the needs and preferences of the people who could benefit from PrEP, and supports uptake, continuation and effective use.

To date, CAB-LA has been implemented only in trial settings. Implementation science is needed to evaluate the feasibility and effectiveness of providing CAB-LA as a choice alongside other PrEP options and HIV prevention services in a range of settings and involving different health cadres. In in-depth interviews (Web Annex F), PrEP providers raised concerns that CAB-LA may lead to a re-medicalization of PrEP services, as many providers now have experience providing PrEP outside of clinic settings (particularly during the COVID-19 pandemic). However, more research is needed to understand the perspectives and needs of the range of providers implementing comprehensive PrEP services that will include CAB-LA. This includes assessing potential restrictions by regulators that may prevent CAB-LA injections being administered by the range of appropriately trained providers, including lay providers, who are central to oral PrEP services.

Furthermore, implementation studies should explore strategies for optimizing the delivery of CAB-LA together with complementary services, such as contraceptive services and gender-affirming care, in the same clinic visit. To support acceptable, effective and efficient services, this research may evaluate different injection schedules and innovative service delivery models such as at-home or in-clinic self-injection of CAB-LA and community-based delivery.

5.6 Population-level impact and costs and cost–effectiveness

Preliminary results of mathematical modelling suggest that increasing the total number of PrEP users, whether of oral PrEP or CAB-LA, has the strongest impact on decreasing HIV incidence (Web Annexes D and E) *(19)*. CAB-LA use itself has the potential to increase the number of HIV infections averted. Models for sub-Saharan Africa also suggest that CAB-LA could be cost-effective even if priced higher than oral PrEP. However, more research on the potential population-level impact, costs and cost–effectiveness of CAB-LA is needed across settings and populations to develop models based on the results of CAB-LA efficacy trials and other data that become available from implementation studies. To date, models have largely considered extreme scenarios of PrEP scale-up and switching to CAB-LA to determine effects; more realistic assumptions are required to inform programmes on impact and cost–effectiveness. Also, no model has considered a PrEP method mix that includes the DVR. Cost–effectiveness studies should also consider additional costs that may be associated with CAB-LA, including costs of different potential HIV testing approaches and schedules.

6. UPDATING AND DISSEMINATION

This guideline is being launched as a web-based product for dissemination and will include all evidence as presented to the GDG (Web Annexes A to F). The guideline will also be incorporated into the periodic updates of the WHO consolidated guidelines on HIV *(3)*. The consolidated guidelines on HIV will be updated in full or in part based on regular scoping exercises of available evidence and experience from country implementation that trigger and guide the need for new guidance. As the evidence base or users' needs change, consideration will be given to producing technical updates such as this document on specific subjects.

WHO headquarters will work closely with its regional and country offices, national ministries of health and implementing partners to plan for dissemination, adaptation and implementation of this new recommendation. Key steps in the dissemination will include presenting the recommendations at international conferences; conducting workshops to support country adaptation; rapidly developing adaptation tools to assist countries in setting priorities for resource allocation so as to facilitate full implementation over time; and conducting briefings and joint planning for dissemination with international and national implementing partners.

To monitor uptake, data will be made available through the WHO country intelligence database, which is updated every six months to reflect changes in policy and implementation for all LMICs and selected high-income countries.

REFERENCES

1. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/186275, accessed 18 May 2022).
2. Guidelines: updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/340190, accessed 18 May 2022).
3. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/342899, accessed 18 May 2022).
4. 2021 UNAIDS Global AIDS Update — Confronting inequalities — Lessons for pandemic responses from 40 years of AIDS. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2021 (https://www.unaids.org/en/resources/documents/2021/2021-global-aids-update, accessed 27 June 2022).
5. United Nations General Assembly. Political declaration on HIV and AIDS: ending inequalities and getting on track to end AIDS by 2030. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2021 (https://www.unaids.org/sites/default/files/media_asset/2021_political-declaration-on-hiv-and-aids_en.pdf, accessed 27 June 2022).
6. Schaefer R, Schmidt H-MA, Ravasi G, Mozalevskis A, Rewari BB, Lule F et al. Adoption of guidelines on and use of oral pre-exposure prophylaxis: a global summary and forecasting study. Lancet HIV. 2021;8:e502-e10.
7. Dubov A, Ogunbajo A, Altice FL, Fraenkel L. Optimizing access to PrEP based on MSM preferences: results of a discrete choice experiment. AIDS Care. 2019;31:545-53.
8. Kuteesa MO, Quaife M, Biraro S, Katumba KR, Seeley J, Kamali A et al. Acceptability and predictors of uptake of anti-retroviral pre-exposure prophylaxis (PrEP) among fishing communities in Uganda: a cross-sectional discrete choice experiment survey. AIDS Behav. 2019;23:2674-86.
9. Minnis AM, Atujuna M, Browne EN, Ndwayana S, Hartmann M, Sindelo S et al. Preferences for long-acting Pre-Exposure prophylaxis (PreP) for HIV prevention among South African youth: results of a discrete choice experiment. J Int AIDS Soc. 2020;23:e25528.
10. Minnis AM, Browne EN, Boeri M, Agot K, Van Der Straten A, Ahmed K et al. Young women's stated preferences for biomedical HIV prevention: results of a discrete choice experiment in Kenya and South Africa. J Acquir Immune Defic Syndr. 2019;80:394.
11. Quaife M, Eakle R, Cabrera Escobar MA, Vickerman P, Kilbourne-Brook M, Mvundura M et al. Divergent preferences for HIV prevention: a discrete choice experiment for multipurpose HIV prevention products in South Africa. Med Decis Making. 2018;38:120-33.
12. Vickerman P, Quaife M, Kilbourne-Brook M, Mvundura M, Eakle R, Terris-Prestholt F. HIV prevention is not all about HIV–using a discrete choice experiment among women to model how the uptake and effectiveness of HIV prevention products may also rely on pregnancy and STI protection. BMC Infect Dis. 2020;20:1-11.

13. Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022;399:1779-89. Erratum in: Lancet. 2022 May 7;399(10337):1778. PMID: 35378077.

14. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med. 2021;385:595-608.

15. FDA approves first injectable treatment for HIV pre-exposure prevention [press release]. Washington (DC): U.S. Food and Drug Administration; 2021 (https://www.fda.gov/news-events/press-announcements/fda-approves-first-injectable-treatment-hiv-pre-exposure-prevention, accessed 27 June 2022).

16. WHO handbook for guideline development, 2nd ed. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/145714, accessed 17 February 2022).

17. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A et al. Going from evidence to recommendations. BMJ. 2008;336:1049-51.

18. Ahluwalia AK, Inzaule S, Baggaley RB, Vitoria M, Rodolph M, Schaefer R et al. Characterization of dolutegravir drug resistance in persons diagnosed with HIV after exposure to long-acting injectable cabotegravir for pre-exposure prophylaxis. Submitted to AIDS, 2022.

19. HIV Modelling Consortium Working Group on Modelling Integrase Inhibitor Drug Resistance in Relation to Injectable Long-acting Cabotegravir Use in Sub-Saharan Africa. Predicted effects of introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study. In preparation.

20. Landovitz RJ, Li S, Grinsztejn B, Dawood H, Liu AY, Magnus M et al. Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial. PLoS Med. 2018;15:e1002690.

21. Markowitz M, Frank I, Grant RM, Mayer KH, Elion R, Goldstein D et al. Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial. Lancet HIV. 2017;4:e331-e40.

22. Landovitz R, Donnell D, Kallas E, Magnus M, Marzinke M. Updated efficacy, safety, and case studies in HPTN 083: CAB-LA vs. TDF/FTC For PrEP. Conference on Retroviruses and Opportunistic Infections (CROI); virtual, 2022.

23. Dmitrov D HJ, Meyer-Rath G, A P. Cost-effectiveness modelling. Unpublished.

24. Marzinke MA, Grinsztejn B, Fogel JM, Piwowar-Manning E, Li M, Weng L et al. Characterization of human immunodeficiency virus (HIV) infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. J Infect Dis. 2021;224:1581-92.

25. HIV drug resistance database [website]. Menlo Park (CA): Stanford University; 2022 (https://hivdb.stanford.edu/, accessed 27 June 2022).

26. Meyer-Rath G. Cost-effectiveness modelling. Unpublished.

27. Blair CS, Li S, Chau G, Cottle L, Richardson P, Marzinke MA et al. Hormonal contraception use and cabotegravir pharmacokinetics in HIV-uninfected women enrolled in HPTN 077. J Acquir Immune Defic Syndr. 2020;85:93.

28. Glaubius RL, Hood G, Penrose KJ, Parikh UM, Mellors JW, Bendavid E et al. Cost-effectiveness of injectable preexposure prophylaxis for HIV prevention in South Africa. Rev Infect Dis. 2016;63:539-47.

29. Quaife M, Terris-Prestholt F, Eakle R, Cabrera Escobar MA, Kilbourne-Brook M, Mvundura M et al. The cost-effectiveness of multi-purpose HIV and pregnancy prevention technologies in South Africa. J Int AIDS Soc. 2018;21:e25064.

30. Smith JA, Garnett GP, Hallett TB. The potential impact of long-acting cabotegravir for HIV prevention in South Africa: a mathematical modeling study. J Infect Dis. 2021;224:1179-86.

31. van Vliet MM, Hendrickson C, Nichols BE, Boucher CA, Peters RP, van de Vijver DA. Epidemiological impact and cost-effectiveness of providing long-acting pre-exposure prophylaxis to injectable contraceptive users for HIV prevention in South Africa: a modelling study. J Int AIDS Soc. 2019;22:e25427.

32. Vogelzang M, Terris-Prestholt F, Vickerman P, Delany-Moretlwe S, Travill D, Quaife M. Cost-effectiveness of HIV pre-exposure prophylaxis among heterosexual men in South Africa: a cost-utility modeling analysis. J Acquir Immune Defic Syndr. 2020;84:173-81.

33. Walensky RP, Jacobsen MM, Bekker L-G, Parker RA, Wood R, Resch SC et al. Potential clinical and economic value of long-acting preexposure prophylaxis for South African women at high-risk for HIV infection. J Infect Dis. 2016;213:1523-31.

34. Neilan AM, Landovitz RJ, Le MH, Grinsztejn B, Freedberg KA, McCauley M et al. Cost-effectiveness of long-acting injectable HIV preexposure prophylaxis in the United States: a cost-effectiveness analysis. Ann Intern Med. 2022;175:479-89.

35. Ahmed K, Baeten JM, Beksinska M, Bekker L-G, Bukusi EA, Donnell D et al. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. Lancet. 2019;394:303-13.

36. Luo R, Fong Y, Boeras D, Jani I, Vojnov L. The clinical impact of point-of-care infant diagnosis for HIV: a systematic review and meta-analysis. Lancet. 2022. In review.

37. Otto AO, Rivera CG, Zeuli JD, Temesgen Z. Hepatotoxicity of contemporary antiretroviral drugs: a review and evaluation of published clinical data. Cells. 2021;10:1263.

38. National Institute of Allergy and Infectious Diseases (NIAID). Safety, tolerability and acceptability of long-acting cabotegravir (CAB LA) for the prevention of HIV among adolescent males - a sub-study of HPTN 083. Identifier: NCT04692077. (2020, February – 2023, May). Washington (DC): National Institutes of Health, U.S. National Library of Medicine; 2020 (https://www.clinicaltrials.gov/ct2/show/NCT04692077, accessed 18 May 2022).

39. National Institute of Allergy and Infectious Diseases (NIAID). Safety, tolerability and acceptability of long-acting cabotegravir (CAB LA) for the prevention of HIV among adolescent females - a sub-study of HPTN 084. Identifier: NCT04824131. (2020, November – 2024, May). Washington (DC): National Institutes of Health, U.S. National Library of Medicine; 2020 (https://www.clinicaltrials.gov/ct2/show/NCT04824131, accessed 18 May 2022).

ANNEX. PROCESS FOR DEVELOPING THE GUIDELINES

Methods for synthesizing evidence

WHO's Department of Global HIV, Hepatitis and STI Programmes developed this guideline according to WHO standards and requirements for guideline development, 2nd edition, 2014 *(1)* and under the oversight of the WHO Guideline Review Committee.

The Secretariat within the WHO Department of Global HIV, Hepatitis and STI Programmes coordinated the guideline development process, which was informed by the WHO Guideline Steering Group composed of staff members from the Department of Sexual and Reproductive Health, Department of Research for Health and at least one representative from each region.

To inform these guidelines, WHO conducted a systematic review of the safety, efficacy, and effectiveness of CAB-LA as PrEP to reduce the risk of HIV acquisition (Web Annex B), under the leadership of Dr Virginia Fonner (Medical University of South Carolina/FHI360). Dr Lara Lorenzetti worked with Dr Fonner on the review and led the review on the values and preferences (Web Annex C) regarding the use of injectable PrEP, including CAB-LA, to prevent HIV infection. The WHO secretariat and the guideline methodologist, Dr George Rutherford, oversaw the collection, review and grading of evidence.

The HIV Prevention Trials Network (HPTN) Modelling Centre and the HIV Modelling Consortium presented preliminary results from mathematical modelling studies on population-level impact of CAB-LA introduction (Web Annexes D and E) *(2)*. Mary Henderson, an independent consultant, carried out a global survey and in-depth interviews with PrEP providers on their perspectives and preferences regarding CAB-LA for HIV prevention among PrEP providers (Web Annex F). The characterization of dolutegravir cross-resistance in persons diagnosed with HIV after exposure to CAB-LA PrEP was presented by Amrit Ahluwalia of Tufts University *(3)*.

Retrieving, summarizing and presenting the evidence

Quantitative evidence synthesis and evidence to recommendations

The GRADE method was used to rate the quality of the evidence and determine the strength of the recommendations. The GRADE approach to developing recommendations, which WHO has adopted, defines the quality of evidence as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The strength of a recommendation reflects the degree to which the GDG is confident that the desirable effects (potential benefits) of the recommendation outweigh the undesirable effects (potential harm). Desirable effects may include beneficial health outcomes (such as reduced morbidity and mortality), reduction of burden on the individual and/or health services and potential cost saving. Undesirable effects include those affecting individuals, families, communities or health services. Additional considerations include the resource use and cost implications of implementing the recommendations and clinical outcomes (such as drug resistance and drug toxicity). All systematic reviews followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews and meta-analyses.

A list of potential outcomes of interest was circulated among a subgroup of the GDG and then discussed in virtual meetings with the group. Each reviewer independently scored the importance of each outcome on a scale of 1 to 9.1. These scores were averaged to determine the relative importance of each outcome. Outcomes considered critical were used to focus the gathering of evidence, including the systematic reviews, to inform the recommendations.

GDG meeting

The GDG met virtually between the 9th and 10th of March, 2022. The supporting evidence and evidence to decision-making tables were shared in advance of the meeting (Web Annexes A through G). The recommendation was made through consensus, and the discussions were facilitated by the methodologist. Voting was not required but the group agreed at the start of the meeting that 2/3 of votes would be required for a decision.

Peer review

The draft guidelines were circulated for review to members of the GDG and the External Review Group. The WHO Guideline Steering Group reviewed the comments and incorporated them into the final document with due consideration of any conflicts of interest of External Review Group members.

Declarations of interest

All external contributors to the guidelines, including members of the GDG and the External Review Group completed a WHO declaration of interests form in accordance with WHO policy for experts. A brief biography of each GDG member was published on the WHO HIV website for a period of 14 days before the first meeting of the GDG with a description of the objectives of the meeting. No public comments or objections were received.

In accordance with the revised WHO policy for experts, WHO conducted a web-based search of GDG members to identify any potential competing interest. The responsible technical officer reviewed the declaration of interests forms as well as the results of the web-based search for each member of the GDG. WHO contacted individuals for clarifying information and the WHO Office of Compliance, Risk Management and Ethics (CRE) was consulted as needed. After discussion with the CRE, one member was removed due to their conflicts of interests and did not participate in the GDG meeting. A management plan for each declared conflict was agreed and recorded in advance of the meeting. Members of the GDG were also asked to declare any undeclared and/or new conflicts of interest at the start of the GDG meeting.

All declaration of interest forms are on electronic file at the WHO Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes and will be maintained for 10 years.

External Review Group

The responsible technical officers reviewed the declaration of interest forms from members of the External Review Group in accordance with WHO guideline development policy, and the results were shared with the WHO Guideline Steering Group. Any conflicts of interest identified were considered when interpreting comments from External Review Group members during the external review process.

References

1. WHO handbook for guideline development, 2nd ed. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/145714, accessed 17 February 2022).
2. HIV Modelling Consortium Working Group on Modelling Integrase Inhibitor Drug Resistance in Relation to Injectable Long-acting Cabotegravir Use in Sub-Saharan Africa. Predicted effects of introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study. In preparation.
3. Ahluwalia AK, Inzaule S, Baggaley RB, Vitoria M, Rodolph M, Schaefer R et al. Characterization of dolutegravir drug resistance in persons diagnosed with HIV after exposure to long-acting injectable cabotegravir for pre-exposure prophylaxis. Submitted to AIDS, 2022.

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