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REVIEW ARTICLE

Long-acting injectable cabotegravir for PrEP: A game-changer in HIV prevention?

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Email: jade.ghosn@aphp.fr**Abstract**

Background: Long-acting injectable cabotegravir (CAB-LA) represents a new additional option for HIV prevention in people at substantial risk of HIV infection that may fill the gaps in pre-exposure prophylaxis (PrEP) uptake, adherence, and retention in users having difficulty with oral PrEP. Data from clinical trials demonstrated that CAB-LA was safe, highly effective, and well-accepted for HIV prevention. However, the occurrence of breakthrough HIV infections despite timely injections, HIV seroconversion timing and patterns, risk of selection and dissemination of resistance-associated mutations to integrase inhibitors, complexity of follow-up, logistical considerations, and its cost effectiveness compared with oral PrEP constitute significant issues for the integration of CAB-LA into clinical routine.

Findings: These concerns need to be addressed before moving forward with large-scale implementation programmes. Pilot and implementation projects are required in the following areas: HIV testing algorithms, patient education, clinic procedures, protocols for switching and discontinuation, efficacy and safety in populations not included in clinical trials, and demedicalization processes. The development of models to increase the uptake of, adherence to, and persistence with and after CAB-LA injections will also be of paramount importance for success. Lessons learned from these projects will increase experience, staff expertise, and organizational and training capacities to support the roll-out of this new agent as part of HIV prevention programmes.

Conclusion: CAB-LA has not yet achieved its full potential in HIV prevention, and strong commitment from all stakeholders is required to push CAB-LA as a game-changer in HIV response.

KEYWORDS

HIV pre-exposure prophylaxis, long-acting antiretroviral drugs

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INTRODUCTION

Over the last 10 years, pre-exposure prophylaxis (PrEP) for HIV has become the most important breakthrough in HIV prevention strategies. Randomized controlled trials have shown that oral tenofovir disoproxil (TDF)-based PrEP was highly effective for the prevention of HIV infection if adherence was high [1–4]. This led the World Health Organization (WHO) to recommend its use in all individuals at substantial risk of HIV infection in 2015 [5]. After several years, compelling arguments suggest that PrEP deployment has contributed to a decrease in HIV incidence at the community level. In Australia, rapid and targeted PrEP roll-out among 3700 high-risk men who have sex with men (MSM) in a network of 21 clinical sites across New South Wales led to a 31.5% decline in recent HIV infections after 1 year [6, 7]. Rolling out PrEP into HIV prevention programmes became a major priority of HIV prevention policy-makers, but there is still a long way to go to reach the Joint United Nations Programme on HIV/AIDS (UNAIDS) goals. In 2022, ~2.5 million people used PrEP worldwide, which represents only 7% of the new global 2025 target [8, 9]. PrEP barriers are multi-dimensional and occur at each step of the PrEP care continuum [10]. Social, economic, and political interventions remain crucial to addressing these hurdles, but new PrEP regimens are also needed to improve PrEP adherence and acceptance. Long-acting agents and extended-release formulations are being developed to enhance PrEP adherence and coverage. These include long-acting (LA) injectables and oral agents, subcutaneous LA implants, and neutralising monoclonal antibodies [11]. In December 2021, the US Food and Drug Administration (FDA) approved LA cabotegravir (CAB-LA) for HIV prevention in the wake of the HPTN 083 and 084 clinical trial results [12]. The product is administered by providers as a single 600-mg intramuscular injection given at 2-month intervals after an initial two injections 1 month apart. As the first injectable antiretroviral drug (ART) available for PrEP, CAB-LA has the potential to be a game-changer in HIV prevention, but its positioning in the current HIV PrEP strategy remains to be defined.

EFFICACY OF CAB-LA FOR HIV PREVENTION

CAB is an integrase strand transfer inhibitor (INSTI) with potent antiviral activity against HIV. CAB is available both as a short-acting oral formulation and as an LA injectable suspension comprising solely active drug nanocrystals. Non-human primate models demonstrated the high effectiveness of CAB-LA for the prevention of

simian immunodeficiency virus or simian-human immunodeficiency virus acquisition after repeated rectal, vaginal, penile, and intravenous challenges [13–16]. These studies also established the first correlate of protection to develop pharmacokinetic studies in humans. A concentration above four times the protein-adjusted concentration required for 90% viral inhibition ($PAIC_{90}$) was considered as protective. The safety, tolerability, and pharmacokinetics of CAB-LA among people without HIV was assessed in the HPTN 077 and ÉCLAIR studies [17, 18]. These phase II, randomised, double-blinded, placebo-controlled trials assessed different CAB-LA dosing and injection schedules. CAB-LA 600 mg administered in the gluteal muscle every 8 weeks (after an initial 4-week injection interval) met blood pharmacokinetic targets for both male and female study participants, was well tolerated, and resulted in limited laboratory abnormalities [18]. Pharmacokinetic analyses showed that CAB persisted in the plasma for months after the last injection. Plasma CAB concentration decreased below the lower limit of quantification after a median time of 44 and 67 weeks for male and female participants, respectively [19]. These data informed the two randomised, double-blinded, placebo-controlled, clinical trials, which assessed CAB-LA efficacy for HIV prevention in men and women (Table 1). In HPTN 083, 3992 MSM without HIV and 570 transgender women who have sex with men at substantial risk of HIV infection were randomized to either CAB-LA plus TDF-emtricitabine (FTC) placebo or active TDF-FTC plus CAB-LA placebo at 43 sites in Africa, Asia, Latin America, and the USA [20]. All participants received a 5-week oral lead-in period with daily CAB or TDF-FTC. After a median follow-up of 1.4 years, 13 new infections occurred in the CAB group (incidence 0.41 per 100 person-years [PY]) versus 39 in the TDF-FTC group (incidence 1.22 per 100 PY). CAB-LA had a superior effectiveness for the prevention of HIV infection than daily TDF-FTC (hazard ratio [HR] 0.34; 95% confidence interval [CI] 0.18–0.62), with a 66% relative HIV risk reduction. In the first 1-year unblinded period, CAB-LA effectiveness remained unchanged, with 11 additional HIV infections in the CAB-LA group (incidence 0.76 per 100 PY) versus 31 with TDF-FTC (2.20 per 100 PY) (HR 0.33; 95% CI 0.17–0.66) for a similar reduction in HIV incidence [21]. The HPTN 084 clinical trial used a similar design to evaluate the efficacy of CAB-LA among 3224 women aged 18–45 years at risk of acquiring HIV in seven countries in sub-Saharan Africa. After a median of 1.24 years, 40 incident infections were observed in the CAB-LA arm (incidence 0.20 per 100 PY) compared with 36 in the TDF-FTC arm (incidence 1.85 per 100 PY). CAB-LA was shown to be superior to TDF-FTC for the prevention of HIV infection

TABLE 1 Summary of phase III clinical trials on CAB-LA for HIV pre-exposure prophylaxis.

Study	Design	Population	Study sites	Sample size / follow-up	HIV incidence rate with CAB-LA ^a	HIV incidence rate with TDF ^a	HIV relative risk reduction (95% CI)
HPTN 083	Double-blind, randomized controlled non-inferiority trial	Men and transgender women who have sex with men at-risk for HIV	43 sites across Africa, Asia, Latin America, and the USA	4570: 2282 CAB-LA, 2288 daily TDF-FTC Median follow-up: 1.4 years	0.41	1.22	66% (38–82)
HPTN 084	Double-blind, randomized controlled superiority trial	Women at risk for HIV, age 18–45 years.	20 sites in 7 sub-Saharan African countries	3224: 1614 CAB-LA, 1610 daily TDF-FTC Median follow-up: 1.24 years	0.20 (0.06–0.52)	1.85 (1.3–2.57)	88% (69–95)

Abbreviations: CAB-LA, long-acting injectable cabotegravir; FTC, emtricitabine; TDF, tenofovir disoproxil.

^aper 100 person-years (95% confidence interval).

TABLE 2 Occurrence of adverse events in phase III clinical trials.

Trial and events	CAB-LA	TDF/FTC
Any adverse events ^a		
HPTN 083	2106/2280 (92%)	2216/2282 (93%)
HPTN 084	1487/1614 (92%)	1486/1610 (92%)
Serious adverse events		
HPTN 083	120/2280 (5%)	121/2282 (5%)
HPTN 084	33/1614 (2%)	33/1610 (2%)
Injection site reactions		
HPTN 083	1724/2118 (81%)	652/2082 (31%)
HPTN 084	577/1579 (37%)	163/1516 (11%)
Annual weight gain		
HPTN 083	+1.23 kg	+0.37 kg
HPTN 084	+ 2.4 kg	+2.1 kg

Abbreviations: CAB-LA, long-acting injectable cabotegravir; FTC, emtricitabine; TDF, tenofovir disoproxil.

^aGrade 2 adverse event or higher.

(HR 0.12; 95% CI 0.05–0.31), with a 89% HIV relative risk reduction [22]. These two clinical trials established the proof of concept that a single long-acting agent was efficacious in the prevention of HIV infection and clearly support the widespread use of CAB-LA for HIV prevention in both men and women at substantial risk of HIV infection.

CAB-LA SAFETY FOR HIV PREVENTION

In HPTN 083 and 084, CAB-LA was not associated with an increased risk of serious or grade ≥ 2 adverse events compared with TDF-FTC. Injection site reactions (ISRs) were the most common adverse events. In HPTN 083, they were reported in 81.4% of the participants in the CAB-LA group and in 31.3% of those receiving TDF-FTC (Table 2). This led to study discontinuation among 50 participants (2.4%) receiving CAB-LA. In HPTN 084, the rate of ISRs was lower: 38% and 11% of women in the CAB-LA and TDF-FTC arms, respectively. No women stopped PrEP because of ISRs during the trial. In both studies, the ISR rates significantly declined over time. HPTN 077 did not show evidence of significant weight gain compared with placebo [23], but CAB-LA was associated with a significant but not clinically meaningful weight gain in HPTN 083 and 084. In HPTN 083, the mean annualised increase in body weight was 1.23 kg per year with CAB versus 0.37 kg with TDF-FTC. This difference was mainly driven by weight loss in the TDF-FTC group in the first year of the trial. In HPTN 084, both groups showed weight gain, with a mean increase of 2.4 kg per year in the CAB group compared with 2.1 kg per year in the TDF-FTC group ($p = 0.04$). In HPTN 084, the incidence of pregnancy was low (1.3 per 100 PY) and did not appear to differ significantly by study group (29 in the CAB arm; 20 in the TDF-FTC arm) [24]. All pregnancy-associated adverse events were classified

as unrelated to the study product, and no congenital anomalies were observed.

THE PROMISE OF CAB-LA FOR HIV PREVENTION

CAB-LA constitutes a new choice for HIV prevention that may change the PrEP field at different stages. It may convince more individuals to start PrEP, increase users' adherence, and promote PrEP persistence. Several surveys among individuals at high risk of HIV acquisition showed a strong interest in LA injectable agents, notably among those perceiving oral PrEP as too burdensome [25]. The reduction in stigma with the use of injections also appears to be a determinant in the choice to use an LA agent [26]. Thus, CAB-LA may be perceived as an easier and appealing way to take PrEP, which may engage more people in HIV prevention programmes. Furthermore, CAB-LA can address the challenges with adherence to oral PrEP. Clinical trials demonstrated that HIV reduction risk was strongly correlated to users' adherence to oral PrEP [27, 28]. A recent meta-analysis including 43 917 participants estimated that suboptimal adherence concerned 38% of users within the first 6 months [29]. Factors associated with low adherence include younger age, low education level, low perception of HIV risk, poverty, housing instability, or PrEP cost [30]. As CAB-LA makes PrEP simpler and easier for some users, the adherence rate in some settings may be significantly improved. In the same way, this new injectable agent can enhance PrEP use over time. Indeed, in the aforementioned meta-analysis, 41% of users discontinued PrEP within 6 months [29]. It was estimated that, in the USA, only two in every five users persisted on oral PrEP after 2 years [31]. Although individuals may change their risk behaviour over time, it is unlikely that behaviour modifications accounted for such a high level of PrEP cessation. This also reflects lassitude and demotivation regarding oral regimens. As a result, many people who stop PrEP remain at high risk of HIV infection [32]. Switching to injectable PrEP would be an efficient way to increase PrEP persistence in those users. As an additional option for HIV prevention, CAB-LA can definitely fill the gap in adults and adolescents at substantial risk of HIV infection who do not feel comfortable with oral PrEP, who face adherence challenges, or who experienced oral PrEP fatigue. However, some issues still need to be addressed to support the deployment of this new injectable PrEP agent into clinical routine.

ISSUES ABOUT CAB-LA IN HIV PREVENTION

Incomplete efficacy in preventing HIV infection

In HPTN 083 and 084, the superiority of CAB-LA over TDF-FTC was mainly driven by low adherence of study participants with oral PrEP. In the TDF-FTC arm, the proportion of samples with a tenofovir concentration consistent with daily dosing was 74% and 42% in HPTN083 and 084, respectively. This resulted in a 1.2% HIV incidence among MSM who received TDF-FTC. This incidence should be taken in relation to other cohort studies, which reported an HIV incidence among MSM using oral PrEP of <0.2% [6, 7, 33]. This incidence is even lower than those observed with CAB-LA (0.76%) among MSM. Therefore, the superiority of CAB-LA compared with oral PrEP should be interpreted carefully, as it depends on the context. Besides, in the combined blinded plus unblinded analysis of HPTN083, 7 of 25 new HIV infections in the CAB-LA group occurred in participants who received continuous and timely CAB injection. This corresponded to an incidence of 0.15 per 100 PY compared with an overall HIV incidence on CAB-LA of 0.54 per 100 PY. Plasma CAB concentration in those participants was \approx 8-fold the PA-IC₉₀ at the time of infection, above the protective threshold established in the non-human primate models [34]. No explanation has yet been identified, and a careful analysis of these cases is ongoing. These findings indicate that CAB-LA may be less effective than a well-taken oral TDF-based PrEP in MSM. Indeed, breakthrough HIV infections occurring among PrEP users adherent to oral PrEP remains rare and mainly related to a virus carrying resistance to FTC, TDF, or both. Less than 10 cases have been reported out of 2 million users worldwide [34]. This discrepancy in efficacy may limit the implementation of CAB-LA, notably in settings where users are compliant with oral PrEP. In discrete choice experiments, PrEP efficacy significantly weighed on users' decisions when dealing with new treatments [35]. As a result, some users may perceive CAB-LA as less effective and desirable than oral PrEP and could be reluctant to start or switch for this new regimen. Interestingly, the HIV incidence with CAB-LA was lower in HPTN 084, and no breakthrough HIV infection occurred among women receiving timely injections. Compared with men, women have a slower CAB-LA absorption, resulting in a 32% longer terminal-phase half-life [19, 36]. It is unclear whether this pharmacokinetic variability can account for the difference in HIV incidence between the sexes. This discrepancy may also be driven by a higher number of exposures among MSM and transgender

women who have sex with men since the per-event incidence within each group is unknown. The longer terminal half-life was also associated with unsplit injection, higher body mass index, and shorter needles [36]. Polymorphism in enzymes metabolising CAB-LA may also affect the pharmacokinetics of the drug [37]. Additional research will be needed to better understand the variability of the tail phase between different populations.

Timing and patterns of seroconversion

CAB-LA substantially alters the timing and patterns of HIV seroconversion. This finding has already been reported in oral PrEP clinical trials [36], but it appears to be more pronounced with CAB-LA. In HPTN 083, HIV detection was delayed in 11 of 16 infections among participants randomised to CAB-LA (68.8%) [38]. Detection of infection was delayed in the four baseline cases (mean delay 62 days) and in 7 of the 12 incident cases (mean delay 98 days). For these 11 cases, study sites failed to detect infection at one or more study visit using third-generation rapid diagnostic tests. Almost all of these infections would have been detected at an earlier visit using a nucleic acid test (NAT). This could have allowed a faster initiation of ART, which may reduce the risk of INSTI resistance [39]. An HIV testing algorithm based on NAT is being evaluated in the open-label extension study of HPTN 083 and 084. This approach is now recommended by the US FDA and Centers for Disease Control and Prevention (CDC) guidelines [12] and could represent a major pitfall in the implementation of CAB-LA, particularly in low- and middle-income countries.

Emergence of INSTI resistance

Three situations can result in resistance-associated mutations (RAM) to INSTI: (i) CAB-LA initiation during undiagnosed primary HIV infection, (ii) undiagnosed breakthrough HIV infection despite continuous and on-time injection, (iii) breakthrough HIV infection during the tail phase. In HPTN 083, of the 16 HIV infections (4 prevalent, 12 incident) in the CAB-LA group, resistance to INSTI was reported among five participants: one participant had undetected baseline HIV infection and selected INSTI resistance after one CAB injection, two participants had selected resistance during the oral lead-in period, and two participants were infected despite timely CAB-LA injections and had INSTI resistance after receiving four CAB-LA injections [38]. These mutations reduce the susceptibility to the WHO first-line ART regimen based on dolutegravir and pose significant issues. At

the individual level, mutations to INSTI reduce the treatment options and may require the use of a second-line ART regimen based on protease inhibitors for all failures on CAB-LA PrEP. At a collective level, a potential risk of dissemination of such resistance exists. Although it is difficult to estimate, the rise of INSTI resistance could be very impactful in a population of PrEP users mostly covered by CAB-LA. In a recent modelling study led by the HIV Modelling Consortium, widespread usage of CAB for PrEP in sub-Saharan countries could likely lead to an increase in INSTI resistance, with an estimated 5% INSTI resistance rate (upper uncertainty limit 30%) in individuals initiating ART by 2030 compared with 0.5% if CAB-LA PrEP was not introduced [40]. Thus, the absolute number of people living with HIV with integrase inhibitor resistance may be expected to increase even if CAB-LA introduction sharply reduces the incidence of HIV.

Concerns with the tail phase

Dealing with the tail phase also challenges CAB-LA providers and users. After the last injection, CAB concentration in the plasma slowly decreased until the lower limit of quantitation after a median time of 44 weeks for males and 67 weeks for females [19]. During this period, drug concentration might be too low to prevent HIV infection but sufficient to select INSTI resistance in case of HIV infection. To reduce this risk, HPTN 083 and 084 clinical trial participants who discontinued injections received open-label daily TDF-FTC for 48 weeks.

The emergence of INSTI resistance may vary during the tail phase according to the concentration of CAB-LA in plasma. The first months after the last injection could be the riskiest period. Nevertheless, no RAMs to INSTI were detected among users who seroconverted during the tail phase in HPTN 083 [20, 21], but we should bear in mind that this risk may have been underestimated in clinical trials, since it may have happened among participants lost to follow-up.

Logistic and cost considerations

Logistic considerations may also significantly hamper CAB-LA implementation. Intramuscular injections of LA agents in the buttocks to treat HIV infection remains a burden in many centres. Extending CAB-LA to those without HIV will require staff time, financial support, and logistical reorganisation of HIV prevention care. In resource-limited settings, oral PrEP demedicalization processes, aimed at providing PrEP outside medical facilities by a broader range of care providers, have been effective

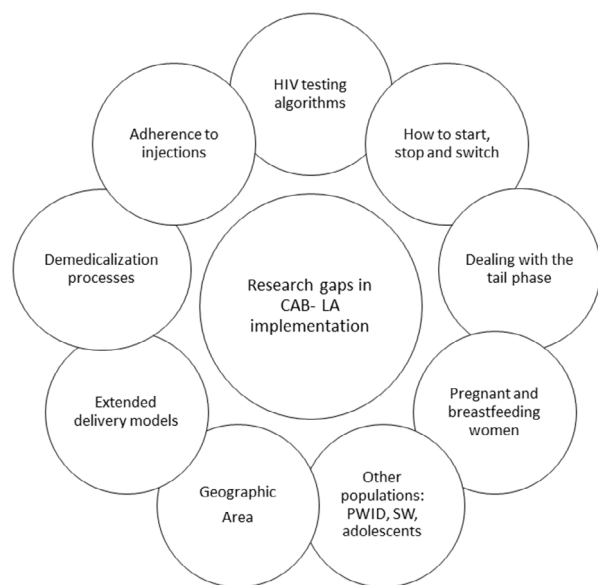


FIGURE 1 Research gaps in cabotegravir (CAB-LA) implementation for HIV prevention. Abbreviations: PWID, people who inject drugs; SW, sex workers

in facilitating PrEP deployment in many countries. The WHO proposed this approach in its most recent recommendations for HIV prevention, treatment, and care [41]. As CAB-LA requires more important supervision for injections and HIV monitoring, this strategy may not achieve such a high demedicalization level as for oral PrEP, which represents an additional barrier for its uptake in HIV prevention programmes. The drug cost also raises concern about accessibility in low- and middle-income countries, which are most in need of this innovation. Generic manufacturers and access initiatives such as the Medicines Patent Pool reduced the price of TDF-FTC to a median cost of ~\$US55 per person per year in 2021 according to the WHO Global Price Reporting. It is likely that the cost effectiveness of CAB-LA will vary according to countries, local drug prices, target populations, CAB-LA interest, and current adherence to oral PrEP. However, as oral PrEP is highly effective, safe, and inexpensive, the additional clinical benefits of CAB-LA cannot justify a large difference in price. Several studies have evaluated the costs or cost effectiveness of CAB-LA or long-acting PrEP. Most focused on the South Africa setting and reported contrasting results, but none incorporated findings from HPTN 083 and 084 in their models [42–45]. More recently, data from HPTN 083 informed a cost-effectiveness analysis conducted in the USA [46]. In this model, CAB-LA for PrEP would be cost effective compared with TDF-FTC generic at 10 years among MSM and transgender women who have sex with men at high risk of HIV in the USA for a price of <\$US1500 per year. Currently, the annual cost for

CAB-LA in the USA is about \$US22 000, 60 times the price of TDF-FTC generics. [Correction added on 29 December 2022, after first online publication: Annual cost for CAB-LA in the preceding sentence has been corrected.] This major cost discrepancy between injectable and oral PrEP is a substantial obstacle to broader roll-out, which could influence the decisions of policy-makers. Advocates demand more pricing transparency and fair agreements to ensure fast and ethical introduction of this new product in HIV prevention programmes. In July 2022, ViiV Healthcare signed a new voluntary licensing agreement with the Medicines Patent Pool for patents related to CAB-LA for HIV PrEP to help access in low-income, lower-middle-income, and Sub-Saharan African countries. This agreement will allow selected generic manufacturers to develop, manufacture, and supply generic versions of CAB-LA for PrEP in 90 countries. This agreement should remove some cost barriers in low- and middle-income countries in the coming years.

In summary, establishing the effectiveness of CAB-LA does not guarantee its uptake into clinical routine. Issues raised in clinical trials need to be addressed in pilot and implementation studies before moving forward with large-scale implementation programmes (Figure 1). Lessons learned during these projects will increase experience, staff expertise, and organisational and training capacities and determine the positioning of CAB-LA as part of HIV prevention programmes.

RESEARCH TARGETS IN THE CAB-LA DEVELOPMENT FOR HIV PrEP

HIV testing algorithm

Defining the most relevant HIV testing algorithms must be a major research priority to support the deployment of CAB-LA. Early detection of breakthrough HIV infection can prevent selection and further dissemination of INSTI-resistance mutations. The CDC recommended an HIV-1 RNA test to monitor PrEP users benefiting from CAB-LA [12]. Although very sensitive for the early detection of HIV infection, this approach remains expensive, not universally available, and usually centrally run. Point-of-care NAT for HIV has been shown to be effective, scalable, and sustainable in improving the HIV care cascade. These rapid and decentralising POC tests hold promise for facilitating monitoring of people living with HIV and potentially CAB-LA PrEP users in low- and middle-income countries. Nevertheless, while several commercial tests exist, those assays are not broadly rolled-out because of implementation and cost challenges. Currently, the WHO estimates that 38% of people living with HIV cannot access

NAT. Therefore, conditioning CAB-LA delivery to a monitoring strategy based on NAT appears unrealistic and will not allow its widespread use. A more realistic approach would be to use NAT only to avoid primary HIV infection at the time of CAB-LA injection. In HPTN 083, screening with NAT close to CAB injections would have detected HIV infection at baseline in all prevalent cases. This procedure has probably the greatest benefit-to-cost ratio and could be easily implemented in countries with wide access to NAT. In case of limited resources, NAT screening could be restricted to individuals most at risk of primary HIV infection that could be identified using specific tools. Pooling samples could also be considered to reduce the cost of NAT, as well as dried blood spot cards, which can facilitate specimen collection and subsequent transport to a central laboratory. Nonetheless, as >95% of all HIV testing worldwide is done at community and health settings without clinical laboratories, it is unlikely that all countries will be able to integrate NAT for HIV screening before CAB-LA injection. Modelling studies are underway to better understand the consequences of maintaining the current HIV testing algorithms based on third-generation HIV tests. In the model developed by the HIV modelling consortium, keeping the current HIV testing algorithm will lead to a rise in INSTI resistance despite a reduction in HIV incidence and in the absolute number of people living with HIV [40]. However, the model suggests that the benefits in terms of reductions in AIDS-related mortality due to CAB-LA will outweigh the risks. These results are yet to be confirmed but strongly support the introduction of CAB-LA, even if NAT testing is not widely available. It is likely that the most relevant HIV testing strategies will vary between countries, depending on the background HIV incidence, healthcare systems, resources, and laboratory facilities. Further research will be needed to determine the type and frequency of HIV testing, as well as the cost-benefit ratio of NAT for CAB-LA initiation and continuation.

How to start, stop, and switch

In clinical practice, prescribers will need to know how to start and stop CAB-LA and how to switch from oral PrEP to CAB-LA and vice versa. Ideally, CAB-LA should be provided for all individuals at substantial risk of HIV infection according to their preferences. However, providers may be reluctant to start CAB-LA in users who may have issues with adherence to injection visits, and cost concerns may lead to the availability of CAB-LA being restricted for people who need it most, i.e., individuals not interested in or with suboptimal adherence to oral PrEP. Identifying those individuals will prove complicated

without specific tools helping providers to assess users' adherence and the potential risk of loss to follow-up. The decision to stop using CAB-LA will also challenge health professionals. How should they deal with users who miss their injections? Should the injections be stopped after one or two missed visits? What conditions must be met to resume treatment? Those questions highlight the need to develop screening and assessment tools and clear guidelines to help providers choose when to start, stop, and/or switch between oral and injectable PrEP.

Follow-up of users

CAB-LA requires careful monitoring of users before, during and after injections to avoid any loss to follow-up and potential breakthrough HIV infection. Ensuring that users will respect the injection schedule will be of paramount importance for implementation. Various clinical and behavioural interventions have been developed to increase PrEP adherence and retention in HIV programmes. These methods include education, counselling, mobile health technologies, patient and peer navigation, case management, or financial incentives. Important progress is still to be made in this field, especially since approaches developed in the oral PrEP field may not be relevant for injectable PrEP. This emphasises the need to develop implementation models across the following areas: patient education, clinic procedures, delivery, methods for and frequency of patient contact, early detection of loss to follow-up, and protocols for switching and discontinuation. Unlike with oral PrEP, user monitoring after CAB-LA discontinuation will be particularly important. Although no cases of RAM to INSTI occurred among individuals who seroconverted during the tail phase in the HPTN studies, this might happen among study participants lost to follow-up. Covering the tail phase using an oral PrEP regimen can prevent this risk. However, this strategy might not work since users have chosen injectable PrEP precisely because they face challenges with oral PrEP. In addition, adequate cover of the tail phase may be self-defeating if its duration exceeds the period of CAB-LA use. Regular HIV testing will be absolutely needed in those individuals, as some may remain at high risk of HIV infection after PrEP discontinuation [32]. The type and frequency of testing remains to be defined and should be adapted to the individuals' risk factors and preferences.

Specific populations

The deployment of CAB-LA requires further evaluation in other populations at substantial risk of HIV

acquisition. The efficacy and safety of CAB-LA have not yet been assessed in people who inject drugs or in transgender men. Notably, no study reported on outcomes related to drug–drug interactions with gender-affirming hormone therapy. Implementation models addressing the needs of sex workers or individuals with overlapping risks of HIV acquisition are necessary. Adolescents and young people face difficulties in adherence and persistence with oral PrEP and constitute a priority population for injectable agents. The safety, tolerance, and acceptability in adolescents (<18 years) is being evaluated in two sub-studies of HPTN 083 and 084, as they have not been included in phase II and III clinical trials. Likewise, limited data exist on CAB-LA administration in pregnant and breastfeeding women. Three pregnancies occurred in HPTN 077 and 49 in HPTN 083. No congenital abnormalities were identified [24]. Despite more pregnancy-related adverse events occurring in the CAB-LA group, none were considered related to the study product. The terminal-phase half-life in pregnant women appeared similar to that in other women. The HPTN 084 open-label extension will allow the accumulation of additional data on pregnancy outcomes with this drug and will use active dosing for CAB-LA to better characterize the pharmacokinetic parameters during pregnancy and breastfeeding. Regarding the potential drug–drug interaction with contraception, a post-hoc analysis of HPTN 077 showed that women on oral contraceptives had a lower peak CAB concentration than those receiving no contraception [22], but the impact of CAB-LA on hormonal contraception has not yet been evaluated.

Demedicalizing injectable PrEP

Oral PrEP roll-out has been made possible with the expansion of differentiated service delivery aiming at providing PrEP outside medical settings by nurse-led, key-population-led, or pharmacist-led models. This simplified and decentralized delivery of PrEP was found to be effective in many countries. PrEP uptake has also been accelerated by its integration in other interventions and services, such as sexually transmitted infection testing, contraception, harm reduction programmes or gender-affirming care. In sub-Saharan Africa, PrEP provision in reproductive health services (family planning, antenatal care, or postnatal care) was proven to be an effective method of PrEP deployment in women [47, 48]. In contrast to oral PrEP, CAB-LA required trained healthcare professionals to perform the injections, clean needles and syringes, and more frequent clinic visits and HIV testing.

This is a major barrier for implementation, particularly in low- and middle-income countries. A first step to support demedicalization processes would be to make self-administration possible for users. Currently, CAB-LA can only be injected in the gluteal muscle, but alternative injection sites are being evaluated [49]. Decentralized and simplified CAB-LA delivery will be of paramount importance for success. Those models must account for the local context, to address barriers identified by both users and providers, and to significantly improve the PrEP care continuum by dealing with retention, adherence, cost, penetration, and sustainability issues. Implementation research studies will be crucial to develop these models and incorporate CAB-LA into clinical practice in ways that meet user, provider, and community perspectives.

INITIATIVES TO SUPPORT CAB-LA DEPLOYMENT

Several initiatives have been developed to coordinate research on CAB-LA implementation and to support a large roll-out. In 2018, a range of stakeholders came together to create the Biomedical Prevention Implementation Collaborative (BioPIC.) This collaborative group includes researchers, civil society, policy-makers, normative agencies, and pharmaceutical companies from over 80 organizations across 20 countries [50]. BioPIC aims to develop a product integration plan to accelerate the deployment of CAB-LA by shortening the time between regulatory approval and large-scale implementation projects. The organization defined a priorities list to introduce CAB-LA rapidly and successfully and coordinate stakeholders' activities to ensure that implementation projects are well-designed to meet the needs of global and country decision-makers. This product introduction framework will be adaptable to next-generation PrEP agents to rapidly convert the results of clinical trials into public health impacts. The Coalition to Accelerate Access to Long-Acting PrEP is a new initiative co-convened by Unitaid, WHO, the UNAIDS, Global Fund, and The United States President's Emergency Plan for AIDS Relief to ensure equitable, timely, and sustained access to longer-acting PrEP options [51]. This coalition, born in July 2022, aims to accelerate the voluntary generic licensing of new PrEP agents through the Medicines Patent Pool, to coordinate implementation science projects via the BioPIC initiative, and to ensure that civil society voices are heard in the deployment of long-acting PrEP agents. This new coalition is expected to accelerate CAB-LA uptake in low- and middle-income countries in the coming years.

CONCLUSION

CAB-LA represents the most important breakthrough in HIV prevention in recent years. This new product is expected to fill the gap of PrEP uptake, adherence, and retention in users having difficulty with oral PrEP. Phase III clinical trials demonstrated that CAB-LA had a better effectiveness than oral PrEP and was safe, effective, and well accepted in HIV prevention among MSM, transgender women, and women. Nevertheless, those trials also brought to light some concerns. The occurrence of breakthrough HIV infections despite timely injections, the timing and patterns of HIV seroconversion, the risk of selection and dissemination of RAM to INSTI, the complexity of follow-up, and the logistical considerations constitute issues for CAB-LA integration into clinical routine. Besides, the cost effectiveness compared with TDF-FTC generics may not support its use at the current price in many settings. Currently, the full potential of CAB-LA is not achieved in HIV prevention as too many constraints curtail its broader roll-out. [Correction added on 29 December 2022, after first online publication: the word 'CAB-LA' has been added in the preceding sentence.] Aware of these difficulties, WHO endorsed CAB-LA as an additional prevention choice for PrEP in its most recent guidelines, pending the results of further studies [52]. Before moving forward, problems raised in clinical trials need to be addressed in pilot and implementation projects in various settings. First, it is necessary to define the most relevant HIV testing algorithm, which must be adapted to context, resources, and facilities. The development of models aiming to increase uptake, adherence, and persistence on and after CAB-LA discontinuation will be of particular importance for roll-out. Furthermore, specific attention must be given across the following areas: patient education, clinic procedures, protocols for switching and discontinuation, efficacy, and safety in other populations and demedicalization processes. A strong commitment from all stakeholders will still be required to move CAB-LA from an innovative tool to a game-changer in HIV prevention. As it stands, this new product is not a panacea in HIV response but represents major progress in the PrEP field.

AUTHOR CONTRIBUTIONS

Geoffroy Liegeon drafted the article, and Jade Ghosn revised the article and approved the final version to be submitted for publication.

CONFLICT OF INTEREST

No conflict of interest declared.

DATA AVAILABILITY STATEMENT

The data that support this review article are available in PubMed.

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