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SUPPLEMENT ARTICLE

Barriers to Uptake of Long-Acting Antiretroviral Products for Treatment and Prevention of Human Immunodeficiency Virus (HIV) in High-Income Countries

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Long-acting injectable antiretroviral therapy (LAI-ART) for the treatment and prevention of human immunodeficiency virus (HIV) holds great potential to shift treatment paradigms by offering an alternative to daily oral medication. However, significant challenges at the drug, patient, and system levels risk impeding the uptake and implementation of LAI-ART. This review aims to describe the known and anticipated barriers to uptake of LAI-ART in high-income countries, as well as the ongoing research addressing some of these barriers to improve the delivery and uptake of LAI-ART products.

Keywords. antiretroviral therapy; cabotegravir; HIV-1; long-acting injectable antiretroviral; preexposure prophylaxis; rilpivirine.

Despite major advances in the efficacy and tolerability of antiretroviral therapy (ART) for the treatment and prevention of HIV, the Centers for Disease Control and Prevention (CDC) estimates that up to 37% of people living with HIV (PLWH) in the United States remain virally unsuppressed and at risk for transmitting HIV to others [1]. Data from patient cohorts and clinical trials suggest that suboptimal adherence is a key contributor to virologic failure [2]. Long-acting injectable (LAI) formulations of ART provide an alternative to the daily adherence required of current oral ART and offer a new paradigm for the treatment and prevention of HIV. Phase 3 clinical trials demonstrated the safety and efficacy of the first LAI-ART regimens tested for HIV treatment and prevention (Table 1) [3–10], supporting regulatory approval of intramuscular cabotegravir and rilpivirine (CAB/RPV-LA) for HIV treatment, as well as intramuscular cabotegravir (CAB-LA) for pre-exposure prophylaxis (PrEP) by both the European Medicines Agency (EMA) [11, 12] and the US Food and Drug Administration (FDA) [13, 14].

Although LAI-ART can address some of the barriers related to concerns about stigma, privacy, and pill aversion encountered with the use of daily oral therapy, there are implementation challenges that will need to be overcome. This review aims to describe the known and anticipated barriers to uptake of LAI-ART for the treatment and prevention of HIV in high-income countries.

DRUG-LEVEL BARRIERS

Some barriers to the uptake of LAI drugs are due in part to the intrinsic properties of the currently approved formulations. An understanding of these barriers will be important for clinician education and appropriate patient selection.

Oral Lead-In Dosing

The fact that many long-acting antiretrovirals (ARVs) cannot be withdrawn once administered leads to concerns over the risk of adverse effects, including allergic reactions and idiosyncratic reactions like hepatotoxicity. One strategy to address this barrier uses an oral lead-in period of drug dosing to assess safety and side effects. The CAB/RPV-LA treatment studies required initial dosing of both CAB and RPV orally once daily for 4 weeks prior to parenteral dosing [3–8], whereas the CAB-LA prevention studies required initial oral dosing of CAB for 5 weeks [9, 10].

The ATLAS study found that side effects during the oral lead-in period were infrequent [4]. Similarly, the FLAIR study reported no drug-related hypersensitivity events or drug-induced liver injury through 96 weeks of follow-up [6]. In a continuation of the FLAIR study, 232 participants originally randomized to the oral control arm were transitioned to CAB/RPV and given the option to choose between the 4-week oral lead-in (48% of participants) or starting LAI-ART immediately ("direct-to-inject" approach, 52% of participants). Over 6 months, adverse events and efficacy were similar in each group leading investigators to conclude that direct-to-inject is an "effective initiation strategy" [15].

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Table 1. Clinical Efficacy Trials of Long-Acting (LA) Injectable Antiretroviral Therapy (ART) for Treatment and Prevention of HIV

Study	Trial Design	Study Population	Treatment Arms	Response Rate	Summary
ATLAS [3, 4]	Phase 3, randomized, multicenter, open-label, noninferiority switch trial	Adults with HIV on ART with suppressed HIV RNA (N = 616)	Continue daily regimen (2 NRTI + [PI, NNRTI or INSTI]) vs CAB 30 mg daily + RPV 25 mg daily × 4 w oral lead-in followed by CAB-LA 600 mg IM × 1 + RPV-LA 900 mg IM × 1 at week 4 followed by CAB-LA 400 mg IM + LA RPV 600 mg IM Q4W beginning at week 8	HIV-1 RNA level <50 copies/mL: Week 48: 92% in LA arm vs 95% in oral arm Week 96: 100% in LA arm and 97% in switch arm	CAB/RPV-LA IM Q4W noninferior to standard oral ART
FLAIR [5, 6]	Phase 3, randomized, multicenter, open-label, noninferiority trial	ART-naive adults with HIV (N = 629)	*Oral induction* (all participants): DTG/ABC/3TC daily × 20 w *Maintenance regimen*: Continue daily oral regimen vs Oral lead-in CAB 30 mg daily + RPV 25 mg daily × 4 w followed by CAB-LA 600 mg IM × 1 + RPV-LA 900 mg IM × 1 at week 4 followed by CAB-LA 400 mg IM + RPV-LA 600 mg IM Q4W beginning at week 8	HIV-1 RNA level <50 copies/mL: Week 48: 94% in LA arm vs 93% in oral arm Week 96: 87% in LA arm vs 89% in oral arm	CAB/RPV-LA IM Q4W noninferior to standard oral ART
ATLAS-2M [7, 8]	Phase 3b, randomized, multicenter, open-label, noninferiority switch trial	Adults with HIV on ART with suppressed HIV RNA (N = 1045)	CAB-LA 400 mg IM + RPV-LA 600 mg IM Q4W vs CAB-LA 600 mg IM + RPV-LA 900 mg IM Q8W	HIV-1 RNA level <50 copies/mL: Week 48: 94% in Q8W arm vs 93% in Q4W arm Week 96: 91% in Q8W arm vs 90% in Q4W arm	CAB/RPV-LA IM Q8W noninferior to Q4W regimen
HPTN 083 [9]	Phase 2b/3, randomized, multicenter, double-blind, double-dummy, noninferiority trial	Cisgender MSM and transgender women who have sex with men at risk for HIV (N = 4570)	Oral TDF/FTC daily vs CAB 30 mg daily × 5 w oral-lead in followed by CAB-LA 600 mg IM Q8W	Incident HIV infections: Week 153: 13 in the CAB-LA arm (0.41 per 100 person-years) vs 39 in TDF/FTC arm (1.22 per 100 person-years)	CAB-LA IM Q8W superior to daily oral TDF/FTC for HIV prevention among MSM and transgender women
HPTN 084 [10]	Phase 3, randomized, multicenter, double-blind, double-dummy, noninferiority trial	Cisgender women aged 18–45 y at risk for HIV (N = 4570)	Oral TDF/FTC daily vs Oral lead-in: CAB 30 mg daily × 5 w oral lead-in followed by CAB-LA 600 mg IM Q8W	Incident HIV infections: Interim planned analysis: 4 in the CAB-LA arm (0.2 per 100 person-years) v 36 in the TDF/FTC arm (1.86 per 100 person-years)	CAB-LA IM Q8W superior to daily oral TDF/FTC for HIV prevention among cisgender women

Abbreviations: ART, antiretroviral therapy; CAB-LA, long-acting cabotegravir; HIV, human immunodeficiency virus; IM, intramuscular; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV-LA, long-acting rilpivirine; TDF/FTC, tenofovir disoproxil fumarate–emtricitabine.

Another potential adverse consequence of the oral lead-in arose in the HPTN 083 PrEP study, in which 3 participants acquired incident HIV infections during this period, highlighting the adherence challenges of this strategy [9]. In current drug prescribing information, both the EMA and FDA support the choice of either an oral lead-in or a direct-to-inject strategy.

Drug Injections

The recommended dosing of CAB/RPV-LA for HIV treatment is two 3 cc injections administered at separate gluteal injection sites (either on opposite sides or at least 2 cm apart on the same side) initially, followed by maintenance injections every month (two 2 cc injections) or every 2 months (two 3 cc injections). The ATLAS 2 M study compared monthly dosing with every 2-month dosing of CAB/RPV-LA and found safety and efficacy were similar, supporting current EMA and FDA recommendations for this simpler administration schedule (every 8 weeks) [7, 8]. Missed injection doses of LAI-ART can be managed with a temporary transition to oral dosing. This "bridging" strategy was shown to be effective in a small group of participants in the FLAIR study [5]. In the current drug labeling for CAB/RPV-LA, both the EMA and FDA outline strategies to address missed doses [11–14].

A pooled analysis from week 48 data across the ATLAS and FLAIR studies counted a total of 3663 injection site reactions (ISRs), representing 25% of all injections administered [16]. Most of these were mild to moderate in severity, and <1% were grade 3 (severe) or greater. Incidence of ISRs was highest with the first dose and decreased with time (70% initially vs 16% by week 48) and most (88%) resolved within 7 days. Injection site pain was the most commonly reported ISR (21% of injections), with nodules, induration, and swelling noted less frequently. Despite the relative frequency of ISRs, they led to only 1% of participants discontinuing treatment.

Data from early trials of CAB-LA for HIV prevention had similar findings of frequently reported ISRs that were of low

severity, with minimal impact on overall medication discontinuation or decreased participant satisfaction. Adverse event frequency was similar between study arms in HPTN 083 [9]. ISRs were reported in 81% of participants in the CAB-LA arm but were mild or moderate in severity and decreased over time. Only 2% of participants who received at least one CAB-LA injection discontinued the injections due to an ISR. Serious adverse events were uncommon (5%) and balanced between study arms. Results were similar for women enrolled in the HPTN 084 study for PrEP, in which 21% of participants experienced any ISR and no participants discontinued therapy due to an ISR [10].

To address injection site reactions as a potential barrier to uptake, patients should be counseled on the possible discomfort from receiving ART injections, particularly with the initial dose, and on strategies to ameliorate symptoms, such as the application of cold or warm packs, the use of over-the-counter pain relievers, or massage of the affected area. Several additional drug formulations are under investigation: a more concentrated formulation of CAB-LA that would halve the required injection volumes; addition of a hyaluronidase preparation that would allow for a higher injected volume; intramuscular thigh preparations that would enable self-injection, and subcutaneous dosing of CAB-LA.

Drug–Drug Interactions

Drug–drug interactions are common with some oral antiretroviral drug classes and long-acting formulations may complicate their management. For example, several important drug interactions affect the combination of CAB/RPV-LA, and prescribers should be aware of the primary mechanisms of enzyme induction and inhibition, which may lead to virologic failure or toxicity.

Drugs that induce uridine diphosphate glucuronosyltransferase (UGT)1A1 or cytochrome P450 3A4 may decrease the concentrations of both CAB and RPV and should not be used concomitantly with LAI products to avoid the risk of causing a loss of virologic response [13, 14]. These include some anticonvulsants (eg, carbamazepine, oxcarbazepine, phenobarbital, phenytoin), antimycobacterials (eg, rifabutin, rifampin, rifapentine), systemic glucocorticoids (eg, more than a single dose of dexamethasone), and herbal supplements (eg, St. John's wort).

Other co-administered drugs may interact with LA preparations through enzyme inhibition, leading to toxicity. Rilpivirine may prolong the QT interval, especially at supratherapeutic levels and should therefore be used with caution in conjunction with drugs which may increase rilpivirine concentrations, and in particular those which also have the potential to prolong the QT interval (eg, clarithromycin) [13]. Because most of these interactions were described with oral formulations, interactions could be different with long-acting formulations and require further study.

Drug Resistance

LAI-ART formulations by their design provide prolonged plasma and tissue drug concentrations following cessation of dosing, producing a "pharmacokinetic tail" which could lead to selection of drug-resistant viral strains. For example, in the HPTN 077 study of CAB-LA for HIV prevention, 23% of male and 63% of female participants had cabotegravir concentrations detectable at 52–60 weeks after the final injection, and modeling suggests some men would have detectable cabotegravir concentrations for up to 3 years and some women up to 4 years after the final injection [17]. Interestingly, in HPTN 083, no cases of cabotegravir resistance were linked to the "pharmacokinetic tail" period, although 4 of 9 incident HIV cases had integrase inhibitor resistance documented—2 during the oral lead-in period and 2 while receiving injectable cabotegravir with expected drug concentrations [9].

In a large pooled analysis of 1039 participants receiving CAB/RPV-LA in the phase 3 treatment studies, virologic failure occurred in 1.25% of subjects [18]. In each of the treatment studies, a small number of participants (1%) experienced virologic failure with both new non-nucleoside reverse transcriptase inhibitor resistance and integrase inhibitor resistance.

The way to manage the risk of resistance varies—for people on LAI-ART, the first goal is to minimize treatment interruptions and use short-acting oral drug formulations (either oral formulations of the long-acting agents or standard oral regimens) as necessary, as outlined in prescribing information from the EMA and FDA. An additional consideration for prevention is that people transitioning off LAI-PrEP with ongoing HIV exposure risk should be prescribed short-acting oral PrEP (eg, emtricitabine in combination with either formulation of tenofovir) for at least a year (and probably longer) while the long-acting drug concentrations wane.

PATIENT-LEVEL BARRIERS

Barriers to uptake also occur at the patient level. LAI-ART must be suitable for the needs of the individual patient, while addressing their concerns.

LAI-ART Perceptions in Special Populations

Although HIV affects people of all ages, genders, ethnic groups, and income levels, some populations experience a significantly higher risk of infection or face unique barriers to the uptake of HIV treatment and prevention. For example, although adolescents and young adults comprise only a small fraction of the total number of persons living with diagnosed HIV, almost a quarter of new HIV diagnoses in the United States in 2018 occurred in young people ages 13–24 years [19]. In the United

States, the HIV epidemic disproportionately impacts racial and ethnic minority populations, with a higher incidence and prevalence seen in Black and Latinx persons [20]. Cisgender women have historically been underrepresented in HIV research and face unique barriers in HIV prevention, with PrEP use among women in high-income countries disproportionately low compared to their prevention need [21]. Gender and sexual minorities, in particular men who have sex with men (MSM) and transgender women, experience a higher incidence of HIV infection than their heterosexual and cisgender counterparts [22]. People who use drugs (PWUD) are yet another population vulnerable to HIV for whom LAI uptake may pose unique challenges, and in which use of LAI-PrEP has not been directly studied in clinical trials [23].

Attention to the perceived barriers to uptake of LAI products for HIV treatment and prevention will be critical in minimizing further disparities in care and addressing the needs of vulnerable populations. The following sections summarize the current data available for different populations.

Adolescents and Young Adults

Clinical trials have demonstrated the safety and efficacy of LAI-ART in adolescents and young adults, with the FDA recently approving CAB/RPV-LA for treatment of adolescents 12 years of age and older in March 2022 [13]. However, research to optimize implementation and uptake in this population is still needed. A survey among youth aged 13–24 living with HIV found an overall high rate of probable or definite willingness to use LAI-ART (88%), with youth with an HIV viral load >1000 copies/mL and female participants who had past experiences with implantable contraceptive methods showing higher levels of LAI-ART acceptance [24]. Notable barriers included frequency of injections and perceived side effects, with the proportion of respondents endorsing definite willingness to use LAI-ART significantly higher with decreased injection frequency compared to more frequent injections.

Regarding LAI-PrEP, a study on the preferences for on-demand and long-acting PrEP among sexual and gender minority adolescents found convenience, duration, and ease of access to play important roles in adolescents' preferences, with parents being viewed as a barrier to taking PrEP regardless of delivery method due to their roles in adolescents' ability to access healthcare [25]. Early data from the phase I/II IMPAACT 2017 (MOCHA) trial found that IM administration of CAB-LA or RPV-LA in adolescents achieved target exposure concentrations consistent with predictions, with no new or unanticipated safety concerns identified [26]. Of the 23 participants enrolled at time of analysis, only 2 premature treatment discontinuations of the study drug occurred: 1 due to hypersensitivity (after the first oral dose) and 1 due to pain with needle insertion prior to receiving the first IM injection. Expansion of adolescents' access to preventive services, education inclusive of PrEP information, and parent-supported PrEP conversations could reduce barriers to adolescent PrEP uptake.

Black and Latinx

Using long-acting contraceptives and antipsychotics as a historical backdrop, health care providers have historically been more likely to offer LAI formulations of these products to Black patients under the assumption that they are at higher risk for non-adherence [27]. Insistent offering of a long-acting medication rather than utilizing methods to encourage and support adherence to oral medications may lead to medical mistrust and a perception of paternalistic control [28]. Although studies on the topic are not representative of all Black individuals, research indicates that this barrier can be overcome if providers build trust and address patient concerns [27]. It is possible that the use of LAI-PrEP among Black and Latinx communities will mirror the low uptake of oral PrEP seen in these populations [29]. Social and structural barriers that already exist for oral PrEP may persist, or even expand in the early rollout of LAI products. Medical mistrust remains a pervasive barrier to engagement with HIV prevention services among Black and Latinx individuals [30].

Cisgender Women

Research on uptake of LAI-ART in cisgender women appear to be promising, although barriers still remain. A multicenter study consisting of interviews with women living with HIV noted a number of facilitators of LAI-ART uptake [31]. However, concerns around medical mistrust, fear of potential side effects, and the burden of additional medical visits for administration were cited as likely challenges to LAI-ART uptake.

Interviews with a group of women from the Women's Interagency HIV Study (WIHS) about interest in LAI-PrEP found that few women expressed interest in PrEP in general [21]. When prompted to choose a regimen, 55% preferred LAI options, 10% opted for daily pills, and 33% said they would not take PrEP regardless of formulation. Barriers cited in this study included medical mistrust, with a fear of new (and perceived untested) injectable products, concern regarding administration location and potential side effects, and feasibility of accessing LAI sites at the frequency needed. With data on efficacy and tolerability in women accruing, future studies should incorporate more women, especially younger women and those in high-risk groups, to explore unique concerns and facilitate uptake.

Men Who Have Sex With Men (MSM)

In an online survey of 2241 self-identifying MSM participants, LAI-PrEP products with perceived severe side effects were rated to be the most significant barrier to uptake, although potential users would probably tolerate mild-to-moderate side effects [32]. The burden of out-of-pocket costs was also a frequently cited concern. Reduction of injection frequency was considered

to marginally increase likelihood of PrEP utilization in this study. Service location and potential negative judgement/stigma were relatively less important barriers of concern compared to other LAI-PrEP attributes in this population.

People Who Use Drugs (PWUD)

Studies of other long-acting treatments for alcohol or opioid use disorder have suggested that PWUD often discontinue treatment after three months [23]. Research on barriers to uptake of PrEP in PWUD points to a disconnect between risk-taking and risk perception among PWUD, with nearly two-thirds (62%) reporting being satisfied with their current HIV prevention strategy [23]. Perhaps the largest barrier to uptake is a general lack of awareness of LAI-PrEP options. Interviews with 234 HIV-negative individuals with opioid use disorder and self-reported HIV risk behaviors recruited from Connecticut's largest addiction treatment program found that only 26% of participants were aware of LAI-PrEP (compared to 67% who had heard of oral PrEP). Acceptance did increase following a description of LAI-PrEP, with 73% reporting willingness to use it if it were made available to them. As with other key populations, potential barriers included concerns regarding efficacy, safety, and cost, with potential long-term side effects being the most commonly cited concern in this group (77%).

Transgender Women

LAI-antiretrovirals could be a particularly valuable option for transgender women, in whom oral PrEP uptake has historically been low due to social, structural, and clinical barriers. Although study of perceived facilitators and barriers to the uptake of LAI-ART among transgender women is limited, research suggests that transgender women feel CAB-LA injections could help to overcome challenges with PrEP adherence [33]. However, transgender participants have expressed concern about the standard gluteal injection site, since some transgender women use buttock implants and fillers as part of their gender-affirming care [34]. Concern around CAB-LA requiring a healthcare provider to inject CAB-LA and fear of potential pharmacologic cross-interactions with gender-affirming hormone therapy has also been cited [33, 34].

In a series of interviews with transgender women in New York City about perceived barriers and preferences for tailoring injection delivery strategies to administer CAB-LA for PrEP, findings suggested the need to offer CAB-LA to transgender women through multiple delivery protocols, such as self-injection or "drop-in" centers [35]. Participants endorsed alternative delivery methods that enhanced injection convenience and allowed for a degree of privacy, free from judgement.

Populations Without Data

Early uptake of LA-ART is limited in certain sub-populations, because safety and efficacy data are still unavailable for a number of key demographics. For instance, safety and efficacy of LAI-ART during pregnancy and while breastfeeding remains under investigation. Data on the safety and pharmacokinetics of CAB-LA in women enrolled in HPTN 084 who became pregnant (n = 29) found that residual CAB-LA was generally well tolerated [36]. Ongoing studies will examine the safety and pharmacology of CAB-LA in women who chose to continue CAB-LA through pregnancy. Studies are also still ongoing for LAI-ART in children under the age of 12 years. Early treatment trials of CAB/RPV-LA have also excluded patients with hepatitis B virus (HBV) coinfection, as well as patients with prior virologic HIV failure or ongoing viremia. No data are available on the efficacy of injectable therapy in people with gluteal implants or soft tissue fillers. Ongoing research is evaluating LA-ART use in these and other important groups, including PWUD, which may enhance future uptake of LA-ART for select populations.

SYSTEM-LEVEL BARRIERS

Despite offering certain advantages over daily oral ART and PrEP, LAI formulations to treat and prevent HIV can be difficult to put into practice, beginning with getting these novel but costly formulations approved by healthcare payers. Even if reimbursed, their successful introduction requires not only an openness on the part of clinicians to alter their treatment approach but also a willingness by healthcare providers, administrators, and staff to adopt the necessary changes within their institution or medical practice to make the transition possible. The literature suggests that there may be a reluctance among members of the healthcare establishment to adopt and meaningfully implement injectable therapy, which would almost invariably require a shift in practice operations. Prior to CAB/RPV-LA receiving regulatory approval, a pre-implementation study among clinical and non-clinical stakeholders in Los Angeles County, California, found a significant level of concern about the potential of LAI-ART to disrupt workflows and place undue demand on workers [37].

Healthcare Personnel Education and Training

As with any new model of medication delivery, there is a current lack of familiarity and experience. For LAI-ART and PrEP to be properly integrated into everyday practice, healthcare personnel must acquire the appropriate knowledge and skills. Without adequate preparation, providers would be poorly equipped to approach their patients about switching to LAI products. Following FDA approval of CAB/RPV-LA, the DHHS HIV/AIDS treatment guidelines were updated in June 2021 to include guidance on LAI-ART [38]. Similarly, the latest update to the HIV PrEP guidelines released by the CDC in December 2021 includes a section about prescribing LAI-PrEP [39]. These guidelines provide recommendations regarding patient selection

criteria, highlight practical considerations when delivering injections, and outline major adverse events and drug interactions. These documents, which will continue to evolve, can serve as a valuable resource to providers, and may prove beneficial toward ensuring a smooth transition.

Clinic Volume and Need for Frequent Injection Visits

One of the ways in which a move to LAI products could have the greatest impact on healthcare operations is the need for more regular follow-up visits, which would in all likelihood translate to an increase in patient volume. Compared with oral medications, which allow for follow-up appointments as infrequently as every six months in the case of ART, or every three months for PrEP, LAI formulations necessitate visits at least every 2 months. An influx of patients risks overwhelming clinic capacity and would require significant additional resources, staffing and space in particular. A streamlined process for overcoming scheduling challenges would be needed for this transition. Ensuring patients, especially those lacking stable housing or transportation, make and keep their appointments will require time and effort by administrative and support staff.

Aside from designing an effective appointment scheduler and reminder system, holding designated clinic sessions, in addition to walk-in hours for patients who have missed their scheduled appointments, might enable practices to manage a larger volume of patients. Future implementation trials and LAI-ART formulations that would allow for self-injection or pharmacy-administered options could also reduce barriers to uptake among patients with difficulty keeping frequent clinic visits.

In addition to increased strain at the system level, a greater number of clinic visits could also be viewed as a barrier at the patient level. In a subgroup of participants from the ÉCLAIR PrEP trial interviewed about CAB-LA, several respondents reported how they would have preferred maintenance injections to occur at a less frequent rate (eg, every 6 months or once yearly) [40]. Patients who frequently travel for extended periods of time may also have difficulty when attempting to access sites for LAI-ART administration.

Medication Procurement and Storage

Practices must also be able to oversee drug procurement and monitor drug supply. Even after the necessary protocols have been established by clinics to efficiently manage the increase in patient traffic, new LAI formulations carry a high cost which must be navigated. For example, with a cost of $3700 per injection, a 1-year supply of cabotegravir for PrEP would cost approximately $22 000 [41]. Although assistance programs can help ease the financial burden for uninsured patients, many cover only the medication itself, not clinic visits or laboratory testing. In an implementation study conducted at the largest Ryan White-funded clinic in the Southeastern United States, providers and administrators ran into significant challenges in their effort to obtain insurance approval for the 28-day oral lead-in and monthly injectable CAB/RPV-LA, which led to delays in initiating treatment, in some cases longer than 4 weeks (if approved at all) [42]. For many patients, regardless of the payer source, the initial insurance claim was rejected, requiring first a prior authorization and then an appeal if the former was denied, both of which take considerable time and effort. Another important consideration is the need to start the process over if patients change insurance providers.

When the medications can be attained, doctor's offices must have the capacity for properly storing them, which is a challenge specific to LAI-ART. Unlike CAB-LA, which can be stored at 2–25°C (and up to 30°C), CAB/RPV-LA requires cold chain storage at 2–8°C in the original carton until ready to administer [13, 14]. Given that the vials can remain at room temperature for up to 6 hours, it is conceivable that some patients may be willing to pick up their dose at the pharmacy and bring it with them to their appointment; however, most patients would likely prefer the convenience of having a pharmacy on-site. Many medical practices, especially those with in-house pharmacies, will already have the appropriate refrigeration equipment to store the medication. However, others will need to invest upfront in the infrastructure needed to manage and dispense these therapies.

Staffing and Space Requirements

Given the requirements for high-volume intragluteal injections using the Z-track method, self-injection is currently not an option [13, 14]. Such being the case, there must also be enough

Table 2. Barriers to Uptake of Long-Acting Injectable Antiretroviral Therapy

Drug-Level Barriers
Oral lead-in period
High-volume gluteal injections
Injection site reactions
Drug–drug interactions
Drug resistance (pharmacologic tail)
Patient-Level Barriers
Frequent clinic visits (at least every 2 m)
Gluteal injection site issues (eg, obesity, buttock implants, tattoos)
Patient access (transportation, insurance)
Lack of efficacy/safety data in children <12 y
Lack of efficacy/safety data in pregnancy/breastfeeding
Lack of efficacy data in patients with prior virologic failure
Adherence requirements
Inability to treat HBV coinfection
System-Level Barriers
Healthcare personnel education and training requirements
Increased clinic volume
Need for cold-chain storage capacity
Drug cost
Staffing and space constraints

Abbreviation: HBV, hepatitis B virus.

Table 3. Ongoing LAI-ART Clinical Trials[a]

Alternative Drug Injection Locations	
NCT04371380	IM injections of CAB/RPV-LA administrated in the vastus lateralis muscle—Phase 1
NCT04484337	IM injections of CAB-LA administered IM (gluteal and lateral thigh) or SC (abdominal)—Phase 1
Special Populations	
NCT03635788	AIDS Clinical Trials Group Study A5359: LATITUDE (Long-Acting Therapy to Improve Treatment SUccess in Daily LifE)—Randomized trial evaluating CAB/RPV-LA in participants with a history of sub-optimal adherence and control of their HIV
NCT04518228	PK properties of ARV and TB drugs (including CAB-LA) administered during pregnancy and postpartum
NCT05154747	LATA (Long-Acting Treatment in Adolescents)—Randomized, open-label trial of CAB/RPV-LA in virologically suppressed HIV-1-positive adolescents aged 12–19 y
Implementation Trials	
NCT03856580	Alternative CAB-LA injection strategies in transgender women evaluating self-injection and injection by a healthcare provider at "drop-in clinics"
NCT04001803	Qualitative Hybrid III implementation study to identify and evaluate strategies for successful implementation of CAB/RPV-LA
NCT04399551	Hybrid type III trial evaluating implementation strategies through continuous quality improvement for CAB/RPV-LA
NCT04863261	Scheduling CAB/RPV-LA alerts in the retention & huddle modules of the CHORUS App
NCT04973254	Hybrid implementation-effectiveness study evaluating CAB/RPV-LA administration outside of the standard doctor's office/clinic in community partner spaces
NCT04982445	GLACIER (Giving Long Acting CABENUVA in an Infusion centER)—Administration of CAB/RPV-LA in infusion centers

Abbreviations: ARV, antiretroviral; CAB-LA, long-acting cabotegravir; HIV, human immunodeficiency virus; IM, intramuscular; RPV-LA, long-acting rilpivirine; SC, subcutaneous; TB, tuberculosis.

[a]www.clinicaltrials.gov.

trained personnel available in clinic at all times to provide injections to patients, which would potentially exacerbate staffing constraints. Batching injection appointments could help mitigate this problem. It has also been proposed that in addition to physicians, other healthcare members such as nurses, pharmacists, and pharmacy technicians be provided the appropriate teaching [37]. Having a larger pool of staff able to dispense the medication would reduce the burden of each individual, although it would also necessitate training on a larger scale.

There is also the matter of space constraints, with a larger volume of patients and need for privacy likely resulting in a shortage of space. One way to get around this problem would be to reconfigure the existing office space. Another option would be to extend office hours. In the long run, providing LAI medications outside the traditional HIV and sexual health clinic setting, such as in pharmacies, infusion centers, food banks, and substance abuse treatment facilities could help free up space in clinics, although privacy concerns related to the current requirement for intragluteal injections would first have to be addressed.

Implementation Concerns

Although the implementation of LAI-ART and PrEP requires a significant degree of adjustment and a great deal of preparation, it has been the real-world experience of healthcare providers and staff both in the United States and Europe that it is acceptable, appropriate, and feasible, even across a wide variety of clinic types [43, 44]. In an implementation study conducted in the United States, in spite of the ongoing coronavirus disease 2019 (COVID-19) pandemic, barriers to LAI-ART and PrEP were found to decrease substantially over time, with the majority of healthcare staff respondents (78%) believing that optimal implementation was achieved in one to three months [43].

CONCLUSIONS

LAI-ART offers a new paradigm for the treatment and prevention of HIV, which can overcome many issues specific to daily oral therapy. However, barriers to the uptake of LAI products threaten efficient and equitable uptake of these products, even in high-income settings (Table 2). Studies of alternative delivery and implementation strategies are currently underway and aim to address some of these barriers (Table 3). Attention to barriers at the drug, patient, and system levels will allow for improved uptake of LAI products for HIV treatment and prevention.

Notes

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