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LEADING ARTICLE

Advances in Long-Acting Agents for the Treatment of HIV Infection

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Abstract
Long-acting antiretroviral therapy holds the promise of new options for human immunodeficiency virus (HIV) treatment beyond the current paradigm of daily oral pills. Of particular interest is their potential role in addressing challenges with adherence to oral therapy and treatment fatigue. Similar to other conditions where long-acting formulations have proven effective such as contraception and mental health, long-acting antiretroviral therapy could provide additional treatment choices to people with HIV. This review provides an outline of the current landscape of long-acting antiretroviral therapy for HIV treatment, both approved and under development, including cabotegravir, rilpivirine, leronlimab, islatravir, albuvirtide, GS-6207, and broadly neutralizaing antibodies. However, there are a number of research gaps for long-acting antiretroviral therapy including issues regarding resistance and understudied populations, and this review highlights some of the challenges that will need to be addressed for clinical implementation of these novel treatment modalities.

Key Points

A large number of injectable, infusible, implantable, and extended-release/long-acting agents are in clinical development for the treatment and prevention of human immunodeficiency virus infection. These include the anticipated imminent approval of long-acting cabotegravir/long-acting rilpivirine for the treatment of human immunodeficiency virus infection

The spectrum of agents, preparations, vehicles, and classes of agents currently in development is reviewed, as well as research and implementation gaps

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1 Background

The substantial advances in antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection led to significant reductions in morbidity and mortality in persons with HIV (PWH) [1]. International guidelines now uniformly recommend the initiation of ART as soon as possible after diagnosis, utilizing a fully suppressive ART regimen [2–4]. For many PWH, this translates into taking a single, well-tolerated, fixed-dosed combination pill once daily. However, the benefit of ART has not generalized to all populations of PWH, mainly because of challenges to durable adherence to daily oral medications. Over one-quarter of individuals initiated on ART experience episodes of non-adherence [5, 6], and only half of all PWH in the USA achieve viral suppression [7], a suboptimal outcome from both an individual health and a public health perspective. Surveys of PWH taking oral ART regimens suggest great interest (> 75%) in switching to long-acting (LA) ART, particularly among those reporting substance use or missing oral treatment doses, with monthly dosing intervals attracting more interest than weekly or biweekly schedules [8–10]. The availability of novel drug delivery options, including parenteral (injection) delivery, could offer PWH the ability to choose a method that best fits their needs, thus increasing adherence to therapy, and potentially improving treatment satisfaction and outcomes [9]. This approach has been shown to be effective in the domains of birth control

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[11, 12], osteoporosis treatment [13, 14], and mental health treatment [15, 16].

In this review, we provide an outline of the current landscape of LA injectable ART (LA ART) including recently approved drugs, those in phase III studies, and those in early development. We also provide an overview of the research gaps that remain unanswered in the field. Last, we focus on the challenges to be addressed for clinical implementation of these novel treatment modalities.

2 Approved Long-Acting Injectables

2.1 Ibalizumab

Though the overall prevalence of multi-drug resistant (MDR) HIV type 1 (HIV-1) infection has declined over the past decade [17, 18], heavily treatment-experienced PWH with MDR strains have limited treatment options and remain vulnerable to poor clinical outcomes. They require the use of new well-tolerated antiretrovirals, with minimal drug interactions and limited cross-resistance to existing agents. Ibalizumab, a humanized IgG4 monoclonal antibody delivered via intravenous infusion, blocks the entry of HIV-1 by noncompetitive binding to CD4, the primary receptor mediating HIV-1 entry [19]. In two phase II studies involving 168 patients with MDR HIV-1 infection, investigators found that ibalizumab at doses ranging from 800 to 2000 mg every 2–8 weeks combined with an individually optimized background regimen including at least one active antiretroviral drug resulted in a reduction in viral load and an increase in CD4 T cells that were maintained through 24 weeks and 48 weeks [20, 21]. In a phase III study enrolling 40 extensively treatment-experienced adults with MDR HIV-1 infection [22], participants received ibalizumab initially as a 2000-mg infusion followed by an 800-mg infusion every 14 days while continuing on an individually optimized background regimen for 24 weeks. At the end of the maintenance period (week 25), 33 patients (82.5%) had at least a 0.5 log10 reduction in HIV RNA, 43% of the patients had a viral load of less than 50 copies/mL, and 50% had a viral load of less than 200 copies/mL. In addition, the safety profile of ibalizumab was reassuring: the adverse events that occurred, regardless of severity or causality, were generally consistent with events expected in patients with advanced HIV/acquired immune deficiency syndrome; with diarrhea (20%) being the most common adverse event. Four participants died from causes related to underlying illnesses not felt to be related to the ibalizumab therapy.

Following the presentation and publication of this study, [22] the US Food and Drug Administration (FDA) approved ibalizumab at the dose/interval used in the phase III study in 2018 under a streamlined approval process for HIV therapies in a population that needs new treatment options [23]. A recent analysis projected cost effectiveness and budget effects of ibalizumab and background ART utilizing data from the phase III trial [24]. Ibalizumab and background ART increased 5-year survival from 38 to 47%, and with an annual combined cost of > US$660,000/year, only became cost effective if the cost of ibalizumab was reduced by over 88%, with no threshold of efficacy at which this combination treatment became cost effective [24]. However, researchers noted that while the treatment was not cost effective, the low number of eligible patients makes the overall impact of adding ibalizumab to an optimized background regimen relatively small in the USA. Currently, the Department of Health and Human Services Guidelines for HIV therapy recommend the use of ibalizumab in patients with a MDR virus without fully active ART options [25]. However, while ibalizumab could provide benefit to PWH with a MDR virus, advanced disease, limited treatment options, the disadvantages of intravenous administration, biweekly dosing intervals, and cost present operational challenges [24].

3 Long-Acting Injectables Currently in Phase II and III Clinical Trials

3.1 Rilpivirine

Rilpivirine (RPV, TMC278), a diarylpyrimidine derivative, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV by the FDA in 2011 when used as part of an oral combination ART regimen [26–28]. In addition to its oral use, the pharmacokinetics and chemical properties of RPV, largely insoluble in water and oils, enabled its development as a nanosuspension [29]. A phase I study of different doses of a RPV nanosuspension aimed at evaluating the pharmacokinetics and safety of gluteal or deltoid intramuscular (IM) injections or abdominal subcutaneous injections in 60 healthy HIV-negative volunteers showed consistent results with the preclinical experience: RPV was slowly released from the injection site into plasma, with drug concentrations of more than 10 ng/mL for 12–26 weeks (with minimal reported adverse events and no grade 4 adverse events) [30]. Its plasma elimination half-life is 44–61 days and sub-therapeutic concentrations have been detected in plasma and female genital fluids over 18 months after a single IM injection [30, 31].

3.2 Cabotegravir

Cabotegravir (CAB, GSK1265744) is an investigational HIV integrase strand transfer inhibitor (INSTI), a chemical congener of dolutegravir (DTG), with comparable in vitro activity and potency [32]. Cabotegravir is under development

primarily in its LA injectable formulation simultaneously for both the treatment and prevention of HIV. A short-acting tablet for oral administration is available currently as a lead-into LA use, but is not planned for independent development. Phase I and IIa double-blind, placebo-controlled studies evaluating single and daily oral CAB doses over 10 days demonstrated dose-proportional increases in drug concentrations in HIV-uninfected participants and PWH, a prolonged mean plasma half-life of 31.5 h, and in PWH, a significant 2.2–2.3 $\log_{10}$ copies/mL decrease in HIV RNA levels over 11 days [33]. Cabotegravir was generally well tolerated with no clinically relevant trends in laboratory values, vital signs, or electrocardiographic changes. A phase I open-label study tested a 200-mg/mL injectable suspension of CAB administered at single increasing doses given either intramuscularly or subcutaneously in HIV-uninfected individuals and found prolonged plasma concentration–time profiles with measurable concentrations of CAB up to 52 weeks after dosing [34].

3.3 Clinical Trials Evaluating Intramuscular Long-Acting Cabotegravir and/or Long-Acting Rilpivirine for the Treatment of Human Immunodeficiency Virus

3.3.1 LATTE, LATTE-2, and POLAR

LATTE (Long-Acting Antiretroviral Treatment Enabling; NCT01641809) was a phase IIb study that evaluated the combination of oral CAB and RPV for use in treatment-naïve PWH (Table 1) [35]. This study randomized 234 PWH 1:1:1:1 to escalating doses of oral CAB (10, 30, or 60 mg) vs efavirenz (EFV), in combination with a 2 nucleoside analog (NRTIs) backbone, for 24 weeks followed by substitution of the 2 NRTI backbone for oral RPV 25 mg daily in those who achieved suppression vs continuation of 2 NRTIs plus EFV for 72 weeks. The study design served as the proof of concept that the two-drug combination of RPV and CAB can maintain virologic suppression for those treated to undetectable concentrations using an oral regimen. In the induction phase, 85–87% of the participants in the oral CAB arms vs 74% in the EFV arm achieved viral suppression (using a threshold of < 50 copies/mL). After conversion to the two-drug CAB plus RPV oral treatment, 68–84% or participants in the oral CAB groups vs 63% in those maintained on two NRTIs plus EFV maintained viral suppression to < 50 copies/mL at 96 weeks, with a lower frequency of treatment-related adverse events in the CAB plus RPV arms. Based on the results of this study, the 30-mg dose of oral CAB was selected for further clinical development and use as induction in the LATTE-2 study [35].

LATTE-2 (NCT02120352) was a randomized phase IIb study of 286 treatment-naïve PWH who received a daily oral induction with abacavir 600 mg plus lamivudine 300 mg (ABC/3TC) plus oral CAB 30 mg for 20 weeks and were randomized 2:2:1 to continuation of daily oral ABC/3TC plus CAB vs IM CAB 400 mg LA plus RPV 600 mg LA every 4 weeks (Q4W) or IM CAB 600 mg LA plus RPV 900 mg LA every 8 weeks (Q8W). After 96 weeks of follow-up, viral suppression to < 50 copies/mL was maintained in 84% of participants on daily oral ABC/3TC plus CAB in comparison with 87% or participants in the Q4W and 94% in the Q8W groups, with two participants experiencing virologic failure in the Q8W arm (one with treatment-emergent resistance mutations to NNRTIs [K103N, E138G, K238T] and INSTIs [Q148R] and phenotypic resistance to RPV, EFV, CAB, raltegravir, and elvitegravir, but conserved sensitivity to DTG) and one in the daily oral arm. Overall, IM CAB LA and RPV LA were well tolerated with 84% of injection-site reactions being categorized as mild. Based on these results, both the Q4W and Q8W dosing schemes were selected for further evaluation in phase III studies [36]. The week 160 results of this study, where participants who successfully completed 96 weeks of daily oral ABC/3TC plus CAB were switched to an optimized IM regimen of their choice (Q4W or Q8W), demonstrated comparable rates between both arms, without any protocol-defined virologic failure after week 48 [37].

POLAR (NCT03639311) will assess the efficacy and safety of IM CAB 600 mg LA plus RPV 900 mg LA Q8W in 100 PWH who will rollover from LATTE and have remained virologically suppressed to < 50 copies/mL on daily oral CAB 30 mg plus RPV 25 mg. In this study, participants will also have the option to switch to oral daily DTG 50 mg plus RPV 25 mg. Participants will be followed for 52 weeks.

3.3.2 FLAIR, ATLAS, and ATLAS-2 M

The First Long-Acting Injectable Regimen (FLAIR; NCT02938520) study is a phase III non-inferiority study that enrolled 629 treatment-naïve PWH. Participants who achieved viral suppression to < 50 copies/mL after 20 weeks of oral daily ART induction with ABC/3TC/DTG were randomized 1:1 to continuation of this oral regimen or switched to IM CAB LA 400 mg plus RPV LA 600 mg Q4W [38]. The 48-week results from FLAIR demonstrated that 94% of participants in the IM CAB LA plus RPV LA arm maintained viral suppression to < 50 copies/mL, in comparison with 93% of participants in the continuation of daily oral ABC/3TC/DTG arm. This met the pre-specified non-inferiority margin for CAB LA plus RPV LA, which was set at 6%. Safety and tolerability of IM CAB LA plus RPV LA were similar to oral daily ABC/3TC/DTG, with 3% vs 1% of adverse events leading to discontinuation in the IM and standard-of-care (SOC)

Table 1 Clinical trials evaluating intramuscular long-acting cabotegravir (CAB LA) and/or long-acting rilpivirine (RPV LA) for the treatment of human immunodeficiency virus (HIV)

Study	Phase	Population	Design	Duration (weeks)	Status	Results	Sponsor(s)	References
LATTE NCT01641809	IIb	Treatment-naïve adults $N=234$	Daily oral CAB (escalating dose) + oral RPV vs 2 NRTI + EFV	96	Active, not recruiting	68–84% in oral CAB arms vs 63% in EFV arms achieved HIV VL < 50 copies/mL	ViiV/Janssen	35
LATTE-2 NCT02120352	IIb	Treatment-naïve adults $N=286$	Induction with oral ABC/3TC + oral CAB followed by IM CAB LA + RVP LA Q4W or Q8W vs continuation of oral ART	96	Active, not recruiting	87% (Q4W) and 94% (Q8W) in the LA ART vs 84% in oral ART achieved HIV VL < 50 copies/mL	ViiV/Janssen	36
POLAR NCT03639311	IIb	LATTE participants $N=100$	IM CAB LA + RPV LA Q8W vs daily oral DTG + RPV	52	Recruiting	N/A	ViiV/Janssen	N/A
FLAIR NCT02938520	III	Treatment-naïve adults $N=629$	Induction with oral daily ABC/3TC/DTG then randomized to IM CAB LA + RPV LA Q4W vs continuation of oral ART	96 (extension phase available)	Active, not recruiting	IM CAB LA + RPV LA non-inferior to continuation of oral daily ABC/3TC/DTG at 48 weeks	ViiV/Janssen	37
ATLAS NCT02951052	III	Virologically suppressed adults $N=616$	Continuation of oral daily ART vs IM CAB LA + RPV LA Q4W	96 (extension phase or transition to ATLAS-2 M)	Active, not recruiting	IM CAB LA + RPV LA non-inferior to continuation of oral daily SOC ART at 48 weeks	ViiV/Janssen	38
ATLAS-2 M NCT03299049	IIIb	Virologically suppressed adults $N=1045$	Randomization from oral SOC to IM CAB LA + RPV LA Q4W vs Q8W OR from IM CAB LA + RPV LA Q4W to continue Q4W vs Q8W	48	Active, not recruiting	IM CAB LA + RPV LA Q8W non-inferior to Q4W IM CAB LA + RPV LA	ViiV/Janssen	N/A
LATITUDE NCT03635788	III	Sub-optimally adherent adults $N=350$	Induction with daily oral SOC ART using conditional economic incentives, then randomization to continuation of oral SOC (without incentives) vs IM CAB LA + RPV Q4W	180	Recruiting	N/A	NIH/NIAID	N/A
MOCHA NCT03497676	I/II	Virologically suppressed children and adolescents $N=155$	Lead-in phase with daily oral CAB, oral RPV or oral CAB + RPV followed by IM CAB LA Q4W, IM RPV LA Q4W or IM CAB LA + RPV LA Q4W	64–144	Recruiting	N/A	NIH/NIAID	N/A
A5357 NCT03739996	II	Virologically suppressed adults $N=74$	Switch from daily oral SOC ART to 2 NRTI + daily oral CAB followed by IM LA CAB Q4W + VRC01-LS Q12W	96	Recruiting	N/A	NIH/NIAID	N/A

3TC lamivudine, *ABC* abacavir, *CAB* cabotegravir, *DTG* dolutegravir, *EFV* efavirenz, *HIV VL* HIV viral load, *IM* intramuscular, *N/A* not available, *NIAID* National Institute of Allergy and Infectious Diseases, *NIH* National Institutes of Health, *NRTI* nucleos(t)ide analog reverse transcriptase inhibitor, *Q4W* every 4 weeks, *Q8W* every 8 weeks, *Q12W* every 12 weeks, *RPV* rilpivirine, *SOC* standard of care

arms, respectively. Regarding participant preferences, 99% of respondents preferred the IM CAB LA plus RPV LA over the daily oral therapy. In total, three participants randomized to IM CAB LA plus RPV LA (all with HIV-1 subtype A1) had confirmed virologic failure with evidence of treatment-emergent resistance for NNRTI (E138E/A/K/T, K101E) and INSTI (L74I, G140R, Q148R) [38].

The Antiretroviral Therapy as Long Acting Suppression (ATLAS; NCT02951052) study is also a non-inferiority, randomized phase III study that is evaluating the continuation of daily oral SOC ART vs CAB LA 400 mg IM plus RPV 600 mg LA IM Q4W in PWH with long-standing virologic suppression on a SOC oral regimen [39]. In ATLAS, 616 PWH with at least 6 months of virologic suppression were randomized 1:1 to each arm. At 48 weeks, 92% vs 95% of participants in the LA IM and SOC arms, respectively, maintained viral suppression < 50 copies/mL, demonstrating non-inferiority of IM CAB LA plus RPV LA Q4W in comparison with the SOC arm (similar to FLAIR, a 6% non-inferiority margin was pre-specified). Similar to FLAIR, tolerability and safety were comparable between both arms (2% adverse events in the SOC arm vs 3% in the IM arm, with 1% of ISRs leading to discontinuation in the IM arm), with higher participant satisfaction in the CAB LA plus RPV LA arm [39]. Virologic failure with NNRTI (E138E/A/K, V108I) and/or INSTI (L74I, N155H) associated mutations was confirmed in three participants in the CAB LA plus RPV LA arm (also all of whom had HIV-1 subtype A/A1), two of which had NNRTI resistance associated mutations at baseline (demonstrated by archived HIV-1 DNA).

ATLAS-2 M (NCT03299049) randomized approximately 1020 PWH with virologic suppression receiving oral daily SOC ART or IM CAB 400 mg LA plus RPV 600 mg LA Q4W (as part of ATLAS) to either IM CAB LA plus RPV LA Q4W or Q8W. Similar to ATLAS, this study was designed to demonstrate non-inferiority and safety of IM CAB 600 mg LA plus RPV 900 mg LA Q8W compared to Q4W IM CAB 400 mg LA plus RPV 600 mg LA, which was recently confirmed after a 48-week follow-up (https://viivhealthcare.com/en-gb/media/press-releases/2019/august/viiv-healthcare-reports-positive-phase-iii-study-results-of-inve/).

Based on the results of FLAIR and ATLAS, a New Drug Application seeking approval for CAB LA 400 mg plus RPV LA 600 mg IM Q4W was submitted to the FDA on 29 April, 2019. On 21 December, 2019, the FDA provided a complete response letter to this application citing reasons related to the chemistry manufacturing and controls, without any new concerns about safety.

3.3.3 ACTG 5359 LATITUDE

While the phase III studies described above demonstrate the efficacy of IM CAB LA plus RPV LA in PWH, they are limited to populations of PWH with long-standing suppression without prior virologic failure or who were treatment naïve. This limits their generalizability to individuals who face barriers to adhere to daily ART, a population in whom LA injectables could be particularly attractive given their de facto delivery of directly observed therapy and removal of requirement for daily oral dosing. The Long Acting Therapy to Improve Treatment Success in Daily Life study (LATITUDE/ACTG A5359; NCT03635788), sponsored by the National Institutes of Health Division of AIDS throughout the AIDS Clinical Trials Group (ACTG), is an ongoing phase III, four-step, 180-week open-label study that will compare treatment efficacy, safety, and durability of CAB LA plus RPV LA Q4W to an all oral SOC daily ART in 350 PWH with documented suboptimal adherence. In LATITUDE, participants will undergo induction with oral daily SOC ART for 24 weeks (Step 1), supported by a compendium of evidence-based adherence support strategies including conditional economic incentives. This will be followed by 1:1 randomization to continuation of oral daily SOC ART or IM CAB 400 mg LA plus RPV 600 mg LA Q4W (with a 4-week induction using oral CAB 30 mg plus oral RPV 25 mg) in those participants who achieved viral suppression to < 50 copies/mL before or at week 20 (Step 2). Randomized participants will be followed for 52 weeks on their assigned injectable or oral regimen, after which they will transition to an additional 52-week follow-up if already taking IM CAB LA plus RPV LA or initiation of an injectable regimen, if randomized to continuation of daily oral SOC ART in Step 2 (Step 3). Participants who received at least one dose of IM CAB LA and RPV LA in Steps 2 and/or 3, but who did not continue on LA injectables (or if LA injectables have not yet been approved by the FDA upon completion of Step 3), will be followed for 48 weeks on oral SOC ART (Step 4) to assure ART provision given the long half-life of the injectable products.

3.3.4 MOCHA

The More Options for Children and Adolescents (MOCHA; NCT03497676) study is an ongoing phase I/II open-label trial that will establish the optimal dosing and assess safety, acceptability, tolerability, and pharmacokinetics of oral CAB, IM CAB LA, and RPV LA in 155 virologically suppressed children and adolescents with HIV infection who are 12 to < 18 years of age. MOCHA includes two cohorts, each with a 4-week oral lead-in phase (either daily oral CAB 30 mg alone or RPV 25 mg alone or the combination of daily oral CAB 30 mg plus RPV 25 mg) followed by either IM CAB 400 mg LA alone or RPV 600 mg LA alone (each for 16 weeks) or the combination of IM CAB 400 mg LA plus RPV 600 mg LA Q4W for 48 weeks. Both cohorts will be followed for an additional 48 weeks after discontinuation

of study products, for a total follow-up of 64–144 weeks. MOCHA will also evaluate parents/caregivers regarding their experience and perceptions of using an injectable treatment regimen.

3.3.5 ACTG A5357

The ACTG 5357 study (NCT03739996) is a phase II study (currently in development) that will assess the safety, tolerability, pharmacokinetics, and antiviral activity of IM CAB LA 400 mg Q4W in combination with the broadly neutralizing antibody VRC07-523LS in 74 PWH with viral suppression. This is a three-step study in which participants will switch their current daily oral ART to a two NRTI backbone plus oral CAB 30 mg for 5 weeks (Step 1) followed by IM LA CAB 400 mg Q4W plus VRC07-523LS (30 mg/kg) administered as an intravenous infusion every 12 weeks both for 48 weeks (Step 2).

3.3.6 Leronlimab (PRO-140)

Leronlimab is a humanized IgG4, κ monoclonal antibody that blocks HIV-1 from entering and infecting immune cells by binding to the C–C chemokine receptor type 5 with high affinity [40]. It is being studied in PWH with a C–C chemokine receptor type 5 tropic virus at baseline as a weekly maintenance monotherapy (NCT02859961), or as part of a salvage regimen in heavily treatment-experienced viremic patients (NCT03902522), administered subcutaneously or intravenously. In early phase studies, both single intravenous and multiple subcutaneous doses of leronlimab have been well tolerated and have shown average reductions in plasma HIV-1 RNA levels of more than tenfold [41–43]. Leronlimab was granted 'Fast Track' designation status by the US FDA.

4 Long-Acting Agents in Early Development

A number of long-acting agents are in early stages of evaluation and development. The weekly injectable fusion inhibitor albuvirtide is a 32-amino acid synthetic peptide analog of the fusion region of HIV gp-41, similar to enfuvirtide with regulatory approvals in China, where it was originally developed [44]. In a phase III trial, 389 treatment-experienced patients were randomized to receive either lopinavir/ritonavir with albuvirtide 320 mg intravenously once weekly or lopinavir/ritonavir plus background NRTIs. After 48 weeks of treatment, 80% of albuvirtide recipients had a viral load of < 50 copies/mL, compared with 66% of controls (difference 14.4%, 95% CI − 3.0 to 31.9) [45]. A subcutaneous formulation is in development that would allow self-administration every 2–4 weeks, with plans to expand clinical trials of the drug globally.

Islatravir (MK-8951) is a first-in-class, nucleoside reverse transcriptase translocation inhibitor with multiple mechanisms of action [46]. Nucleoside reverse transcriptase translocation inhibitors halt elongation of newly reverse transcribed DNA chains via chain termination (both immediate and delayed by conformational changes), and also prevent translocation of RT. A randomized, double-blind, phase IIb study evaluating the safety and efficacy of islatravir plus doravirine (DOR) vs DOR/lamivudine/tenofvoir disoproxil fumarate (DOR/3TC/TDF) enrolled 121 previously untreated people with no known antiretroviral resistance and no active hepatitis B or C [47]. More than 90% were men, three-quarters were white, the median age was 28 years, and 25% had a viral load above 100,000 copies/mL at baseline. During part one of the study, lasting 24 weeks, participants were randomly assigned to receive one of three doses of islatravir (0.25 mg, 0.75 mg, or 2.25 mg) plus DOR and 3TC, or DOR/3TC/TDF. During part two, those who achieved an undetectable viral load (below 50 copies/mL) on the three-drug combination dropped 3TC and continued taking islatravir and DOR as a two-drug regimen through week 48. At 48 weeks, 89.7%, 90.0%, and 77.4% of people taking the respective islatravir doses maintained viral suppression, as did 83.9% of those taking DOR/3TC/TDF. Six participants experienced virological failure: 5/90 (5.6%) in the islatravir group and 1/31 (3.2%) in the DOR/3TC/TDF, though none had HIV-1 RNA > 200 copies or documented resistance to the study drugs. Treatment was generally safe and well tolerated. Planning for phase III trials of the islatravir plus doravirine combination in diverse patient populations is underway and islatravir alone is also being evaluated both as a monthly oral tablet and as a LA subdermal implant for pre-exposure prophylaxis.

GS-6207, an investigational, novel, selective, first-in-class inhibitor of HIV-1 capsid function, whose pharmacological profile is optimized for subcutaneous administration monthly or less frequently, even among those with a broad range of HIV-1 mutants resistant to other antiretroviral classes, including those with naturally occurring polymorphisms conferring resistance to maturation inhibitors [48]. Data from two phase I studies demonstrate that GS-6207 has potent antiviral activity and a potential dosing interval of up to every 6 months [49, 50]. In both clinical studies, GS-6207 was generally well tolerated and no serious adverse events were reported. Gilead will be initiating enrollment of two new clinical trials of GS-6207 in combination with other antiretroviral agents in PWH: a phase II/III study (NCT03739866) in heavily treatment-experienced individuals with multidrug resistant HIV-1, as well as a phase II study (NCT04143594) in

treatment-naïve PWH. GS-6207 will be administered via a 2-week oral lead-in, followed by a subcutaneous injection every 6 months.

Additionally, there are numerous broadly neutralizing antibodies with the potential to have a prolonged interval of administration up to every 6–12 months, multiple and/or polyfunctional mechanisms of action within and between molecules, and possible subcutaneous or intravenous administration routes. UB-421 is an Fc-aglycosylated, non-T cell-depleting, CD4-specific humanized IgG1 derived from the parent murine B4, which binds to discontinuous conformational epitopes on the HIV-receptor complex, including CD4 domain 1, and competitively blocks HIV entry [51]. In an open-label, phase II clinical study, PWH receiving ART with undetectable plasma viremia underwent analytic treatment interruption, with one group receiving weekly UB-421 at a dose of either 10 mg/kg of body weight for eight doses, and a second group receiving 25 mg/kg every 2 weeks [52]. UB-421 monotherapy maintained suppression of plasma viremia (< 20 copies per mL) in the absence of ART for up to 8 weeks in participants receiving 10 mg/kg every week and for up to 16 weeks in participants receiving 25 mg/kg every 2 weeks. Occasional low-level viral blips, which did not require specific treatment, were detected in eight participants (28%). No evidence of HIV resistance to UB-421 was observed, but this small study of short duration has limited power to detect these changes. Future clinical studies with continued monitoring for drug-resistant strains during long-term administration of UB-421 are needed to properly assess this concern.

5 Research Gaps

As with any new therapeutic strategy, the phase III studies of LA injectables for the treatment of HIV infection leave unanswered questions critical to implementation that will require additional research. For agents such as ibalizumab, approved under a streamlined federal review processes with small sample sizes for MDR patients, the collection of post-marketing reporting and pharmacovigilance will be critical in generating a more detailed understanding of its efficacy and safety profile. While the primary endpoint data for both phase III studies of CAB LA plus RPV LA demonstrated non-inferiority with oral SOC, six confirmed virologic failures occurred, all in subtype A/A1 [53]. The underlying mechanism of this remains unclear, though all three of the failures on the LA ART arm in the FLAIR study did have a baseline L74I polymorphism, which is not considered an INSTI resistance-associated mutation by the International AIDS Society US guidelines. However, of all participants tested for the L74I polymorphism in both phase III studies (approximately half of the participants), over 90% still achieved virologic suppression. Though the observed virologic failures occurred among study participants primarily located in Russia, the subtype A virus comprises a large portion of the HIV strains in eastern Africa; understanding the mechanism of this apparent increased number of virologic failures of those using this strategy in subtype A will be critical prior to broad testing or implementation of this strategy in the east African region.

Broadly neutralizing antibodies targeting a variety of viral epitopes have generated tremendous scientific and clinical interest not only as potential substitutes for oral ART, but as potential immunotherapies (as single or combinations of antibodies, or as multi-antigen-specific antibodies) potentially capable of inducing anti-HIV immune responses and/or reservoir reductions [54]. Such antibodies are being engineered for increased breadth of viral coverage and prolonged pharmacokinetics, and are being studied both as intravenous and subcutaneous infusions. However, durable virologic control in the absence of ART has not been achievable with anti-HIV gp120 broadly neutralizing antibodies as a single agent owing to rapid viral rebound and the emergence of resistant mutations, which has prevented even the most potent of these antibodies from achieving ideal efficacy [55–59].

5.1 Unstudied Populations

For all of these agents, there are also key unstudied populations thus far not included in the registrational clinical trials: children, pregnant women, and those with tuberculosis co-infection. In women of child-bearing potential, the benefit of using DTG, and presumptively CAB, is likely to outweigh the small increased risk (0.3% vs 0.1%) of neural tube defects found in a prospective evaluation of > 120,000 deliveries in Botswana among women taking DTG at conception [60]. However, modeling studies have indicated that, compared with other regimens, DTG leads to better outcomes for women and infants because of improved maternal health and fewer perinatal HIV transmissions; [61] subsequently, the World Health Organization has reaffirmed use of DTG for all persons with HIV, including pregnant women [62]. Given the structural similarity of CAB to DTG, a cautious and data-driven approach is warranted. The safety, pharmacokinetics, and pharmacodynamics of the use of CAB LA and RPV LA in pregnancy and breastfeeding still need to be evaluated.

For those with tuberculosis co-infection, the use of CAB, either oral or LA, with rifampin (RIF)-containing regimens is not recommended. Co-administration of steady-state RIF 600 mg with a single dose of oral CAB 30 mg increased CAB

oral clearance by 2.4-fold and decreased CAB area under the curve by 59% compared with CAB administered alone [63]. The impact of RIF on the LA IM formulations of CAB and RPV was evaluated in an in silico study as well as utilizing physiologically based pharmacokinetic modeling [64, 65]. Results indicated that co-administration of RIF 600 mg with CAB LA and RPV LA would likely lead to suboptimal concentrations of both CAB and RPV, with the physiologically based pharmacokinetic models predicting a reduction in both the area under the curve and the trough concentration of LA CAB (41–46%) and LA RPV (82%) following the first maintenance dose when co-administered with rifampicin. In a phase I, single-center, pharmacokinetic study, 15 male participants received oral CAB 30 mg once daily for 14 days in period 1, and oral CAB plus rifabutin 300 mg once daily for 14 days in period 2 with serial pharmacokinetic sampling at days 14 and 28 [66]. Rifabutin had a modest impact on plasma CAB exposure following oral co-administration, resulting in overall plasma CAB trough exposures above the 10-mg oral dose shown to maintain viral suppression in PWH. Given the prevalence of tuberculosis in regions also significantly impacted by the HIV epidemic, investigating additional LA agents or dosage strategies is a considerable research need.

5.2 Resistance

With studies indicating sustained concentrations of both CAB LA and RPV LA over a year after administration, [30, 34, 67] the concern arises regarding the development of class resistance, particularly in those who are intermittently adherent to LA treatment—potentially selecting for resistant viral quasi-species should LA preparations be allowed to decay "uncovered" by stop-gap oral ART coverage. The clinical implications of the prolonged pharmacokinetic tail remain to be determined with post-marketing use and scale-up, particularly with regard to the potential for selection of resistant quasi-species with delays in injection administration without oral "bridging" [68]. As the LA ART strategy may be preferred by those with challenges to daily pills including those with a history of substance use, mental health comorbidities, and incarceration, drug–drug interactions with LA opioid replacement therapy will also require investigation. The LATITUDE (A5359, NCT03635788) study is enrolling PWH who have some of these additional adherence challenges to examine whether the LA ART strategy is superior to continuing an oral regimen.

5.3 Implementation

The investigation and development of effective strategies that will allow for clinical implementation of LA ART in real-world settings should proceed in anticipation of their regulatory approval. First, clinicians will need to consider a patient-centered approach with shared decision making on the benefits vs disadvantages of the LA ART based on their own treatment history, co-morbidities, and tolerability of and interest in an LA treatment strategy. While clinical decision aids are available for other conditions with multimodal treatment delivery options such as contraception, [69] development of such a tool for HIV treatment may also support a shared-decision approach. At the clinic level, the logistics of accommodating the administration of monthly to bi-monthly IM injections will need to be considered: the cost of the injections themselves (currently not defined), expenses related to maintaining the injection supply including refrigeration of RPV, cost of IM supplies, and the clinic workflow of monthly/bi-monthly clinic visits in addition to the medical visits at 6-month intervals. Given the extensive logistic issues involved in integrating LA ART into clinic flow, exploration of non-traditional healthcare delivery models (pharmacies, minute clinics, non-medical venues such as community-based organizations, mobile vans, home visits) will all need to be investigated and evaluated. Moreover, managed care administrators and payers will require demonstration that LA injectable are cost effective (or cost saving) prior to allowing their unrestricted use in the clinic. An implementation study sponsored by ViiV Healthcare that will enroll 115 participants at nine clinic sites around the USA to identify best practices on the implementation of LA ART is currently underway (NCT04001803).

5.4 Baseline Testing

Additionally, the necessity of resistance testing and potentially subtype testing in virologically suppressed PWH or in low- and middle-income countries where resistance testing is not standard will need to be explored. Integrase strand transfer inhibitor resistance remains low with estimates of 7 per 1000 in a longitudinal study from British Columbia, though it was noted that INSTI resistance testing lags behind the uptake of INSTIs among INSTI-treated individuals (only 34% in 2016) [70]. In the ATLAS study, 40 participants previously exposed to RPV but without document history of RPV resistance did not have virologic failure at 48 weeks [39]. For low- and middle-income settings, the refrigeration requirement for LA RPV may hinder its broad implementation. Finally, LA ART implementation protocols will require assessment of hepatitis B status as neither CAB nor RPV treats hepatitis B and thus would need a separate treatment plan if indicated.

6 Conclusions

The first iteration of LA ART, CAB LA combined with RPV LA, is likely to be availabile imminently, pending regulatory approvals. Phase III studies demonstrate promising results

in terms of efficacy, tolerability, and treatment satisfaction with complementary studies underway or planned in special populations including youth and non-adherent populations. Additional LA ART agents and modalities are in development, suggesting a robust portfolio of LA ART options in the future. While a multitude of important questions remain regarding drug–drug interactions, resistance, and use in unstudied populations, implementation planning should proceed given the anticipated approval, interest among PWH to have additional treatment options, and the potential wide-ranging impact on the treatment cascade and global rates of virologic suppression.

Compliance with Ethical Standards

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Conflict of interest Aadia I. Rana has served on an advisory board for ViiV. Raphael L. Landovitz has consulted for and accepted honoraria from Gilead, Merck, and Roche. Karen T. Tashima has served on advisory boards for Gilead and Merck. Jose R. Castillo-Mancilla has no conflicts of interest that are directly relevant to the content of this article.

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