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

Aadia I. RANA, MD[a], **Jose R. CASTILLO-MANCILLA, MD**[b], **Karen T. TASHIMA, MD**[c], **Raphael L. LANDOVITZ, MD MSc**[d]

[a]Division of Infectious Diseases, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama.; [b]Division of Infectious Diseases, School of Medicine, University of Colorado-AMC, Aurora, Colorado.; [c]Division of Infectious Diseases, The Miriam Hospital, Providence, Rhode Island; [d]Division of Infectious Diseases, David Geffen School of Medicine, Los Angeles, California

Abstract

Long-acting antiretroviral therapy (LA ART) holds the promise of new options for 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, LA ART could provide additional treatment choices to people living with HIV. This review provides an outline of the current landscape of LA ART 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 LA ART 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.

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 living with HIV (PLWH).[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 PLWH, 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 PLWH, mainly due to challenges to durable adherence to daily oral medications. Over one-quarter of individuals initiated on ART experience

Corresponding Author/Reprints: Aadia Rana MD, 845 19th St South, BBRB 206, Birmingham, AL 35205, USA, airana@uabmc.edu.

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episodes of non-adherence,[5,6] and only half of all PLWH in the US achieve viral suppression,[7] a suboptimal outcome from both an individual health and a public health perspective. Surveys of PLWH 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 PLWH 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,[11,12] osteoporosis treatment,[13,14] and mental health treatment[15,16]

In this review, we provide an outline of the current landscape of long-acting 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. Lastly, 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-1 infection has declined over the past decade,[17,18] heavily treatment-experienced PLWH 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 human immunodeficiency virus type 1 (HIV-1) by noncompetitive binding to CD4, the primary receptor mediating HIV-1 entry.[19] In two phase II studies involving 168 patients with multi-drug resistant (MDR) HIV-1 infection, investigators found that ibalizumab at doses ranging from 800mg 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 which 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 a 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/AIDS 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 3 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 3 trial.[24] Ibalizumab and background ART increased 5-year survival from 38% to 47%, and with an annual combined cost of >$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 OBR relatively small in the US. Currently, the DHHS Guidelines for HIV therapy recommend the use of ibalizumab in patients with multi-drug resistant virus without fully-active ART options[25]. However, while ibalizumab could provide benefit to PLWH with MDR virus, advanced disease, and 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 (RPV)

Rilpivirine (RPV, TMC278), a diarylpyrimidine derivative, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for 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, rilpivirine's pharmacokinetics and chemical properties, largely insoluble in water and oils, enabled its development as a nanosuspension.[29] A phase I study of different doses of rilpivirine nanosuspension aimed at evaluating the pharmacokinetics and safety of gluteal or deltoid intramuscular injections or abdominal subcutaneous injections in 60 healthy HIV-negative volunteers showed consistent results with the preclinical experience: rilpivirine 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 intramuscular injection.[30,31]

3.2. Cabotegravir (CAB)

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] CAB is under development primarily in its long-acting injectable formulation simultaneously for both treatment and prevention of HIV. A short-acting tablet for oral administration is available currently as a lead-in to LA use, but is not planned for independent development. Phase I and IIa double-blind, placebo-controlled studies evaluating single and daily oral cabotegravir doses over 10 days demonstrated dose-proportional increases in drug concentrations in HIV-uninfected participants and and participants living with HIV (PLWH), a prolonged mean plasma half-life of 31.5 h, and in PLWH, 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 IM CAB LA and/or RPV LA for treatment of HIV (Table 1).

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 PLWH.[35] This study randomized 234 PLWH 1:1:1:1 to escalating doses of oral CAB (10, 30 or 60 mg) versus 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 versus continuation of 2 NRTI + EFV for 72 weeks. The study design served as proof-of-concept that the two-drug combination of RPV and CAB can maintain virologic suppression for those treated to undetectable levels using an oral regimen. In the induction phase, 85%−87% of the participants in the oral CAB arms versus 74% in the EFV arm achieved viral suppression (using a threshold of <50 copies/mL). After conversion to the two-drug CAB + RPV oral treatment, 68%−84% or participants in the oral CAB groups vs. 63% in those maintained on 2NRTI's + EFV maintained viral suppression to <50 copies/mL at 96 weeks, with lower frequency of treatment-related adverse events in the CAB+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 PLWH who received daily oral induction with abacavir 600 mg + 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 + CAB versus IM CAB 400 mg LA + RPV 600 mg LA every 4 weeks (Q4W) or IM CAB 600 mg LA + 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 + CAB in comparison with 87% or participants in the Q4W and 94% in the Q8W groups, with 2 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. IM CAB LA and RPV LA were, overall, 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 + 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 + RPV 900 mg LA Q8W in 100 PLWH who will rollover from LATTE and have remained virologically-suppressed to <50 copies/mL on daily oral CAB 30 mg + RPV 25 mg. In this study, participants will also have the option to switch to oral daily DTG 50 mg + RPV 25 mg. Participants will be followed for 52 weeks.

3.3.2. FLAIR, ATLAS and ATLAS-2M—The First Long-Acting Injectable Regimen (FLAIR; NCT02938520) study is a Phase III non-inferiority study that enrolled 629 treatment-naïve PLWH. 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 switch to IM CAB LA 400 mg + RPV LA 600 mg Q4W[38]. The 48-week results from FLAIR demonstrated that 94% of participants in the IM CAB LA + 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 + RPV LA, which was set at 6%. Safety and tolerability of IM CAB LA + RPV LA were similar to oral daily ABC/3TC/DTG, with 3% versus 1% of adverse events leading to discontinuation in the IM and SOC arms, respectively. Regarding participant preferences, 99% of respondents preferred the IM CAB LA + RPV LA over the daily oral therapy. In total, 3 participants randomized to IM CAB LA + 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 continuation of daily oral standard of care (SOC) ART versus CAB LA 400 mg IM + RPV 600 mg LA IM Q4W in PLWH with long-standing virologic suppression on a standard-of-care oral regimen[39]. In ATLAS, 616 PLWH with at least 6 months of virologic suppression were randomized 1:1 to each arm. At 48 weeks, 92% versus 95% of participants in the LA IM and SOC arms, respectively, maintained viral suppression <50 copies/mL, demonstrating non-inferiority of IM CAB LA + 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% adeverse events in the SOC arm versus 3% in the IM arm, with 1% of ISRs leading to discontinuation in the IM arm), with higher participant satisfaction in the CAB LA + RPV LA arm[39]. Virologic failure with NNRTI (E138E/A/K, V108I) and/or INSTI (L74I, N155H) associated mutations was confirmed in 3 participants in the CAB LA+ 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-2M (NCT03299049) randomized approximately 1,020 PLWH with virologic suppression receiving oral daily SOC ART or IM CAB 400 mg LA + RPV 600 mg LA Q4W (as part of ATLAS) to either IM CAB LA + RPV LA Q4W or Q8W. Similar to ATLAS, this study was designed to demonstrate non-inferiority and safety of IM CAB 600 mg LA + RPV 900 mg LA Q8W compared to Q4W IM CAB 400 mg LA + 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 (NDA) seeking approval for CAB LA 400 mg + RPV LA 600 mg IM Q4W was submitted to the FDA on April 29th, 2019. On December 21st, 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. LATITUDE—While the Phase III studies described above demonstrate the efficacy of IM CAB LA + RPV LA in PLWH, they are limited to populations of PLWH 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 long-acting 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 NIH Division of AIDS throughout the AIDS Clinical Trials Group (ACTG) is an ongoing Phase III, 4-step, 180-week open-label study which will compare treatment efficacy, safety, and durability of CAB LA + RPV LA Q4W to an all oral SOC daily ART in 350 PLWH 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 (CEIs). This will be followed by 1:1 randomization to continuation of oral daily SOC ART or IM CAB 400 mg LA + RPV 600 mg LA Q4W (with a 4 week induction using oral CAB 30 mg + 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 on IM CAB LA + 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 adolescent 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 + 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 + 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 to 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 PLWH with viral suppression. This is a 3-step study in which participants will switch their current daily oral ART to a 2 NRTI backbone + 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 IV 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 (CCR5) with high affinity.[40] It is being studied in PLWH with CCR5 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 lrtonlimab 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 U.S. Food and Drug Administration.

4. Long-Acting Injectables in early development

An additional cadre of 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 (IV) 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 to 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 (NRTTI) with multiple mechanisms of action.[46] NRTTI’s halt elongation of newly reverse transcribed DNA chains via chain termination (both immediate and delayed by conformational changes), and also prevents translocation of RT. A randomized, double-blind phase IIb study evaluating the safety and efficacy of islatravir plus doravirine (DOR) versus 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 and 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 (0.25mg, 0.75mg or 2.25mg) 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 stayed on 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 on 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 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 long-acting subdermal implant for pre-exposure prophylaxis (PrEP).

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 1 studies demonstrate that GS-6207 has potent antiviral activity and a potential dosing interval of up to every six 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 people living with HIV – a Phase 2/3 study (NCT03739866) in heavily treatment-experienced people living with multidrug resistant HIV-1, as well as a Phase 2 study (NCT04143594) in treatment-naïve people living with HIV. GS-6207 will be administered via a two-week oral lead-in, followed by a subcutaneous injection every six months.

Additionally, there are numerous broadly neutralizing antibodies with potential to have 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 and 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, PLWH on ART with undetectable plasma viremia underwent analytic treatment interruption, with 1 group receiving weekly UB-421 at a dose of either 10 mg/kilogram of body weight for 8 doses, and a second group receiving 25 mg/ kilogram every 2 weeks.[52] UB-421 monotherapy maintained suppression of plasma viremia (<20 copies per milliliter) in the absence of ART for up to 8 weeks in participants receiving 10 mg per kilogram every week and for up to 16 weeks in participants receiving 25 mg per kilogram 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 long-acting 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 multi-drug resistant patients, the collection of post-marketing reporting and pharmacovigilance will be critical in generating a more detailed understanding its efficacy and safety profile. While the primary endpoint data

for both phase III studies of CAB LA + RPV LA demonstrated non-inferiority with oral standard of care, six confirmed virologic failures occurred, all in subtype A/A1.[53] The underlying mechanism of this remains unclear, though all 3 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-USA guidelines. However, of all participants tested for the L74I polymorphism in both phase 3 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, 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 (bNAbs), 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 reduction.[54] Such antibodies are being engineered for increased breadth of viral coverage and prolonged pharmacokinetics, and are being studied both as IV and subcutaneous infusions. However, durable virologic control in the absence of ART has not been achievable with anti–HIV gp120 bNAbs 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]

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 (TB) co-infection. In women of child-bearing potential, the benefit of using dolutegravir, and presumptively cabotegravir, 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 on dolutegravir at conception.[60] However, modeling studies have indicated that, compared with other regimens, dolutegravir leads to better outcomes for women and infants because of improved maternal health and fewer perinatal HIV transmissions[61]; subsequently the WHO has reaffirmed use of dolutegravir for all persons living with HIV, including pregnant women.[62] Given the structural similarity of cabotegravir to dolutegravir, 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 TB co-infection, the use of cabotegravir, 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 to CAB administered alone.[63] The impact of RIF on the long-acting IM formulations of CAB and RPV was evaluated in an in silico study as well as utilizing physiologically based pharmacokinetic (PBPK) 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 PBPK models predicting a reduction in both area under the curve and trough concentration of LA cabotegravir (41%–46%)and LA rilpiviring (82%) following the first maintenance dose when coadministered with rifampicin. In a Phase 1, single center PK 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 PK 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 PLWH. Given the prevalence of TB in regions also significantly impacted by the HIV-epidemic, investigating additional LA agents or dosage strategies is a considerable research need.

Resistance—With studies indicating sustained levels 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 long-acting treatment – potentially selecting for resistant viral quasispecies should long-acting preparations be allowed to decay “uncovered” by stop-gap oral ART coverage. The clinical implications of the prolonged pharmacokinetic tail remain to be deteremined with post-marketing use and scale up, particularly with regard to potential for selection of resistant quasispecies 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 long-acting opioid replacement therapy also will also require investigation. The LATITUDE (A5359, NCT03635788) study is enrolling PLWH who have some of these additional adherence challenges to examine whether the LA ART strategy is superior to continuing an oral regimen.

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, tolerability of and interest in an LA treatment strategy. While clinical decision aids are available for other conditions with multi-modal 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, logistics of accommodating the administration of monthly to bi-monthly intramuscular 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 rilpivirine, cost of IM supplies, and the clinic workflow of monthly/bi-monthly clinic visits in addition to the medical visits at six-month intervals. Given the extensive logistic issues involved in integrating LA ART into clinic flow, exploration of non-traditional health care 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 long-

acting 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 9 clinic sites around the United States to identify best practices on implementation of LA ART re is currently underway (NCT04001803).

Baseline testing—Additionally, the necessity of resistance testing and potentially subtype testing in virologically-suppressed PLWH or in low and middle-income countries where resistance testing is not standard will need to be explored. INSTI 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 treat Hepatitis B and thus would need a separate treatment plan if indicated.

6. Conclusion

The first iteration of LA ART, CAB LA combined with RPV LA, is likely to be availability 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 during pregnancy, implementation planning should proceed given the anticipated approval, interest among PLWH to have additional treatment options, and the potential wide-ranging impact on the treatment cascade and global rates of virologic suppression.

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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 HIV infection. These include the anticipated imminent approval of long-acting cabotegravir/long-acting rilpivirine for treatment of HIV -infection. The spectrum of agents, preparations, vehicles, and classes of agents currently in development is reviewed, as well as research and implementation gaps.

Table 1.

Clinical trials evaluating intramuscular long-acting cabotegravir (CAB LA) and/or long-acting rilpivirine (RPV LA) for treatment of HIV

Study	Phase	Population	Design	Duration	Status	Results	Sponsor(s)	Reference
LATTE NCT01641809	IIb	Treatment-naïve Adults N=234	Daily oral CAB (escalating dose) + oral RPV vs. 2 NRTI + EFV	96 weeks	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 weeks	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 weeks	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 weeks (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 weeks (extension phase or transition to ATLAS-2M)	Active, not recruiting	IM CAB LA + RPV LA non-inferior to continuation of oral daily SOC ART at 48 weeks	ViiV/Janssen	38
ATLAS-2M NCT03299049	IIIb	Virologically-suppressed adults N=1,045	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 weeks	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 weeks	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 to144 weeks	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 + VRC01LS Q12W	96 weeks	Recruiting	N/A	NIH/NIAID	N/A

IM: intramuscular; CAB: cabotegravir; RPV: rilpivirine; NRTI: nucleos(t)ide analog reverse transcriptase inhibitor; HIV VL: HIV viral load; EFV: efavirenz; ABC: abacavir; 3TC: lamivudine; DTG: dolutegravir; SOC: standard of care; NIH: National Institutes of Health; NIAID: National Institute of Allergy and Infectious Diseases; N/A: not available.