

## Review Article



# Long-Acting Injectable Antiretroviral Agents for HIV Treatment and Prevention

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## ABSTRACT

Current oral antiretroviral agents provide highly effective treatment for patients infected with human immunodeficiency virus (HIV), and can be used as pre-exposure prophylaxis (PrEP) to prevent new HIV infections. Several single-tablet regimens with excellent antiviral efficacy have dramatically improved the quality of life of patients who can adhere to daily oral therapy. However, there is increasing demand on long-acting injectable antiretroviral agents for patients who cannot take oral agents or feel fatigue related to daily pill burden. Monthly long-acting (LA) cabotegravir (CAB) combined with rilpivirine (RPV) has recently been listed as optimizing agent for maintenance of HIV suppression in treatment-experienced patients whose viral load is undetectable for 3 to 6 months. Novel agents with different mechanism of action and long half-life extending dosing interval are being tested in phase 2 and 3 clinical trials. This review summarizes the data of efficacies and safety profiles of LA CAB with RPV regimen, and also new long-acting injectable antiretroviral agents in pipeline.

**Keywords:** Human immunodeficiency virus; Long-acting; Injectable antiretroviral agents; Pre-exposure prophylaxis

## INTRODUCTION

Combination antiretroviral therapy (ART) significantly reduced morbidity and mortality related to human immunodeficiency virus (HIV) infection, leading to an increased life expectancy of people living with HIV (PLWH) [1]. HIV infection has become a chronic condition requiring lifelong daily oral agents, and PLWH should adhere to daily ART strictly to maintain viral suppression and prevent the emergence of drug resistance [2]. Daily oral ART has built up the risk of inadvertent disclosure, suboptimal treatment adherence and treatment failure, which has contributed to stigma and depression with reminding of HIV status. PLWH has overcome the treatment fatigue with the help of psychiatrists and would prefer therapeutic alternatives [3-6]. Current drug development of ART, which already has strong antiviral efficacy, is focused on improving the safety profile and increasing the convenience of engagement within care. Two-drug regimens have been used with more confidence and satisfaction in PLWH regardless of whether they were treatment-naïve or had experienced antiretroviral drugs (ARVs) [7]. With the development of novel agents having

**Table 1.** Long-acting antiretroviral agents for HIV treatment and prevention under development

Drug name	Drug class	Route of administration	PrEP or Treatment	Drug status
Cabotegravir	INSTI	Oral & IM	Treatment	FDA approved
		IM	PrEP	Awaiting FDA approval
Islatravir	NRTTI	Oral	Treatment/PrEP	Phase 2
		Implant	PrEP	Phase 3
Lenacapavir	Capsid inhibitor	Oral	Treatment	Phase 2
		SC	PrEP	Phase 2

HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; INSTI, integrase strand transfer inhibitor; IM, intramuscular; FDA, Food and Drug Administration; NRTTI, nucleoside transcription translocation inhibitor; SC, subcutaneous.

a longer duration of action and new drug delivery technology such as subdermal implants, nanomedicine injections, subcutaneous pumps, and microneedle patches, long-acting (LA) ART could improve the care of PLWH and address many challenges associated with treatment fatigue [8].

This review will summarize the antiretroviral agents in use and under development as LA injectable formulations and data of efficacies and safety profiles reported with many clinical trials (Table 1). This will also include the introduction to the ongoing or planned clinical trials in the future. Agents like broadly neutralizing antibodies and monoclonal antibodies will not be covered in this review.

## CABOTEGRAVIR: INTEGRASE STRAND TRANSFER INHIBITOR

Cabotegravir (CAB) belongs to a class of integrase strand transfer inhibitors (INSTI) and a structural analogue of dolutegravir (DTG). Its unique physiochemical and pharmacokinetic properties have enabled its formulation both as an oral agent for daily administration and as a long-acting nanosuspension for monthly intramuscular (IM) injection [9]. Injectable CAB is slowly absorbed, reaching maximal concentration by 1 week and its half-life ( $T_{1/2}$ ) is 5.6 – 11.5 weeks [10, 11]. These characteristics have attributed to the clinical development of CAB for both treatment and prevention of HIV infection. It is primarily metabolized by uridine glucuronyl transferase (UGT) 1A1, and therefore it has a low potential for drug-to-drug interaction [11].

The 2-drug regimen of CAB and rilpivirine (RPV), an agent of non-nucleoside reverse transcriptase inhibitors (NNRTIs), has demonstrated potent antiviral activity for the maintenance of viral suppression in both ART-naïve and experienced patients [12-17]. The phase-2 Long-Acting Antiretroviral Treatment Enabling Trial (LATTE) study provided the regimen of oral CAB with RPV has an antiviral activity similar to efavirenz combined with dual NRTIs through week 96 [12]. The LATTE-2 trial enrolled ART-naïve patients who were given oral CAB in combination with RPV treatment and those who achieved viral suppression were randomly designated to continue oral treatment or switch to IM injections of LA CAB with RPV once monthly or once every 2 months [13]. Viral suppression was maintained in 100 (87%) of 115 patients in the 4-week group and 108 (94%) of 115 patients in the 8-week group through week 160, as compared with 47 (84%) of 56 patients who continued oral treatment. Protocol-defined virologic failure was reported in 3 patients (2 in the 8-week group, 1 in the oral treatment group). Serious adverse events were reported in 22 (10%) of 230 patients among the IM group (4-week and 8-week groups) and 7 (13%) of 56 patients among the oral

treatment group, but none were drug-related. Injection-site reactions (ISRs) were mild to moderate and only 1% of patients discontinued the treatment because of ISRs. Week 160 data of the LATTE-2 study presented this LA CAB with RPV regimen maintained viral suppression in 83% of participants [14]. Adverse events were mostly related to IM injection, and most ISRs were mild to moderate, resolving quickly. More than 99% of participants reported preferences for IM therapy over oral treatment.

The phase 3 First Long-Acting Injectable Regimen (FLAIR) and Antiretroviral Therapy as Long-Acting Suppression (ATLAS) trials evaluated the 2-drug regimen of LA CAB with RPV for ART-naïve patients and those suppressed with the current oral regimen, respectively [15-17]. ART-naïve patients received oral induction therapy with DTG/lamivudine (3TC)/abacavir (ABC) for 20 weeks in FLAIR trial [15, 16]. Participants whose viral load was undetectable after 16 weeks of oral induction therapy, were randomized to either continue the current oral regimen or switch to LA monthly therapy following a 4-week oral lead-in therapy with CAB and RPV. The LA CAB with RPV formulation was non-inferior to the current oral ART regimen maintaining viral suppression through week 48 [15]. Confirmed virologic failure (CVF) was similar to both groups, and resistance-associated mutations (RAMs) have emerged against NNRTI and INSTI. Patients with CVF had RPV RAMs in proviral DNA, HIV-1 subtype A6/A1, or body mass index  $\geq 30$  kg/m<sup>2</sup>. At week 124, 1 (<1%) patient in each arm had  $\geq 50$  HIV RNA copies/mL, consistent with non-inferiority demonstrated at week 48 [16]. Adverse events were similar across all groups in severity and frequency, and ISRs were the most common (21% in the injection group) adverse events. ISRs were almost graded 1 or 2 and disappeared in 3 days.

The ATLAS trial was performed in patients who had received oral ART for >6 months and had an undetectable viral load, but those with a history of virologic failure related to INSTI or NNRTI RAMs were excluded [17]. Monthly injectable LA CAB with RPV was administered after oral lead-in therapy. The proportion of participants whose viral load was suppressed <50 copies/mL in the LA injection group (92.5%) was non-inferior to that of standard daily oral therapy (95.5%) and emerged resistance profiles in CVF were similar to that of FLAIR study. Since most participants transitioned to the ATLAS-2M study, 52 patients were included in the week 96 analysis of ATLAS [18]. 100% and 97% in the LA and switch arms maintained viral suppression under 50 copies/mL. No participants met the CVF criteria and no new safety signals were noted.

The ATLAS-2M study compared the LA regimen (CAB 400 mg + RPV 600 mg IM) every 4 weeks to a higher dose of LA regimen (CAB 600 mg + RPV 900 mg IM) with a longer interval of 8 weeks [19]. The efficacy was not different between both groups. LA CAB with RPV was well tolerated, with 98% of ISRs being mild to moderate and disappeared in 3 days. Participants preferred LA injectable regimen to current oral agents and q 8 weeks dosing over q 4 weeks. Data on the compassionate use of LA CAB with RPV in patients with low adherence to oral therapy because of psychological (N = 15) and physical problems (N = 20) including swallowing and cognitive impairment, were presented at the international AIDS conference (IAS) 2020 [20]. They presented that 80% of patients had <50 HIV RNA copies/mL and median CD4 count of 100/mm<sup>3</sup>. Sixty percent achieved an undetectable viral load and most tolerate well to treatment. There was no ISR-related discontinuation. Letendre et al. reported that LA CAB with RPV achieved therapeutic concentrations in the CSF and controlled HIV in CSF effectively, which suggested the regimen's potential of use in patients with HIV encephalitis in a separate study [21].

With the results of these trials mentioned above, LA CAB with RPV is recommended as an optimization option by Department of Health and Human Services (DHHS) guideline for the treatment-experienced patients whose viral load was undetectable on oral therapy for 3 – 6 months, and who agree to visit the clinic frequently to receive the injectable drugs [22].

LA CAB, at a dose of 600 mg given IM once every 8 weeks, reduces the need for daily administration and may provide a useful alternative for HIV pre-exposure prophylaxis (PrEP) [23]. LA CAB was superior to daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) in preventing HIV infection among men who have sex with men (MSM) and transgender women who have sex with men. This trial was finished early since the superiority was demonstrated on review of the results of the first interim analysis. HIV infection incidentally occurred in 52 participants: 13 in the CAB group (incidence, 0.41 per 100 person-years) and 39 in the TDF/FTC group (incidence, 1.22 per 100 person-years) (hazard ratio, 0.34; 95% confidence interval, 0.18 - 0.62). INSTI resistance was observed in the participants who were diagnosed to have HIV infection in the LA CAB group.

## PRACTICAL CONSIDERATIONS FOR IMPLEMENTING LA CAB IN THE REAL WORLD

To achieve success with LA CAB/RPV in the real world, there are 3 things considered: building administration infrastructure, selecting the “right” patient, and accessing the injectable drug. Delivery system with cold-chain supply needs to be established and the LA RPV should be kept stored at 2 - 8°C [24]. To deliver IM injections correctly to the patients, assistance with medication access needs to be provided and each patient should be observed for 15 minutes after injection. Patients also need to visit a clinic more frequently (monthly) and patient reminder systems should be more intensive to ensure adherence. All of these are increasing the burden on clinics and staffs. In addition, the practitioner should select patients appropriate for LA injection therapy carefully. To evade the risks of the emergence of drug resistance, patients need screening for prior INSTI and NNRTI mutations that may compromise the effectiveness of CAB/RPV. PLWH with extensive antiretroviral drug resistance and/or heavily treatment-experienced are not eligible for LA CAB/RPV therapy [15-17]. And also, the injection therapy is contraindicated in patients with pregnancy or planning pregnancy and those with hepatitis B virus (HBV) coinfection unless receiving an active HBV treatment regimen. Coadministration with drugs significantly decreases CAB or RPV drug concentrations is also contraindicated.

Clinicians should also understand the impact of missed or delayed administration of LA therapy on the antiviral efficacy and emergence of HIV resistance. While the rates of virologic failure were low in FLAIR and ATLAS trials, RAMs have emerged in participants who failed LA CAB/RPV, underlining the effect of nonadherence or delayed administration in the real world setting [15-17]. If the missed dose is planned, oral therapy should be started. If unplanned missed doses happen and the time since the last injection is  $\leq 2$  months, CAB 400 mg (2 mL) and RPV 600 mg (2 mL) IM monthly injections need to be administered as soon as possible [25]. If the time since last injection is longer than 2 months, reinstate the patient with the loading dose (CAB 600 mg and RPV 900 mg) and then continue to follow the maintenance dose (CAB 400 mg and RPV 600 mg) IM monthly injection dosing schedule. When a patient considers stopping injectable therapy, transition to a suppressive oral regimen should occur within 4 weeks of the last IM doses.

A 23-gauge, 1.5-inch IM needle is recommended for injection and 2-inch needle is needed in patients with BMI >30 kg/m<sup>2</sup> [26]. Ventrogluteal IM injections (preferred to dorsogluteal IM) should be given on opposite sides if possible, or at least 2 cm apart if the two shots should be given on the same side. Administration costs and prolonged stay in the clinics is also considered, although the cost of this regimen in Korea will be cheaper than that in other countries. A mathematical model on the use of LA CAB in Kenya suggests that LA therapy is cost-effective even in the high cost of LA therapy [27]. There are also unmeasured potential benefits of LA therapy not covered in clinical trials that should be considered.

## ISLATRAVIR (MK 8591): NUCLEOSIDE REVERSE TRANSCRIPTASE TRANSLOCATION INHIBITOR

Islatravir (ISL) belongs to a class of HIV drugs called nucleoside reverse transcriptase translocation inhibitors (NRTTIs). It functions as an immediate chain terminator that inhibits HIV reverse transcriptase (RT) by preventing translocation of the enzyme, and prevents nucleotide attachment onto the viral DNA chain [28-30]. In instances where RT translocation occur, ISL-triphosphate (TP) can act as a delayed chain terminator by causing structural changes to the viral chain. ISL had a potent activity against HIV-1 and multidrug-resistant HIV strains, and has a long  $T_{1/2}$  of 78.5 to 128 hours [31]. In a study of phase 1b trial performed with 30 treatment-naïve patients, single oral doses of 0.5 to 30 mg of ISL reduced plasma HIV RNA levels by up to 1.7 log<sub>10</sub> copies/mL at 10 days, suggesting that weekly dosing and manufacturing of long-acting formulation may be possible [31]. When 56 mg of ISL is administered by subcutaneous (SC) injection, its  $T_{1/2}$  is 198 h and ISL-eluting implant is projected to release adequate ISL-TP for more than 52 weeks [32]. Elimination of ISL is balanced between adenosine deaminase-mediated metabolism and renal excretion, and ISL does not inhibit enzymes like UGT1A1 or cytochrome p450 (CYP) [33]. In addition, it does not inhibit hepatic transporters organic anion transporting polypeptide (OATP) 1B1, OATP 1B3, organic cation transporter (OCT) 1, or renal transporters organic anion transporter (OAT) 1. Therefore, ISL is unlikely to be the victim or perpetrator of drug-drug interactions with commonly co-prescribed medications.

The phase 2b dose-ranging trial of ISL combined with doravirine (DOR) was performed to evaluate its efficacy and safety for treatment-naïve patients [34]. Participants were randomly assigned (1:1:1:1) to receive oral treatment with one of 3 doses of ISL (0.25 mg, 0.75 mg, or 2.25 mg) in combination with DOR and 3TC or to DOR plus 3TC plus TDF once daily with placebo. After at least 24 weeks of treatment, participants taking ISL whose viral load was lower than 50 copies/mL switched to a 2-drug regimen of ISL and DOR. At week 48, 26 (90%) of 29 participants in the 0.25 mg ISL group, 27 (90%) of 30 in the 0.75 mg ISL group, and 24 (77%) of 31 in the 2.25 mg ISL group achieved HIV-1 RNA concentrations <50 copies/mL, compared with 26 (84%) of 31 in the DOR plus 3TC plus TDF group. Two participants in the 2.25 mg ISL group and one participant in DOR plus 3TC plus TDF group discontinued due to adverse events.

The phase 2 randomized, open-label, active-controlled study evaluating the safety and efficacy of oral weekly regimen of ISL (40 mg on days 1 and 2, followed by 20 mg on day 8 and every week thereafter) in combination with lenacapavir (LEN) in virologically suppressed PLWH is currently recruiting participants [35].

With monthly dose of 60 mg oral ISL, the phase 3 trial (IMPOWER 22) is planned to compare the efficacy versus once-daily TDF/FTC in cisgender women and adolescent girls in sub-



Saharan Africa and another trial (IMPOWER-024) in cisgender men and transgender women who have sex with men worldwide is planned [36, 37].

## LENACAPAVIR (GS-6207): CAPSID INHIBITOR

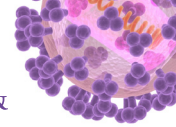
Lenacapavir (LEN) is a capsid-targeting inhibitor of HIV replication. It interferes with multiple early- to late-stage processes of the viral life cycle: capsid disassembly and nuclear transport, virus production, and capsid assembly in a dose dependent manner [38-40]. The capsid (p24) protein surrounds the viral genome and plays a critical role in viral replication. LEN binds to capsid in a pocket between two adjacent capsid monomers. It could inhibit functional disassembly of the capsid shell though stabilizing the capsid shell in early stages of the HIV life cycle. LEN interferes with the transport of viral complexes via the nuclear pore, as it targets the same capsid binding site that helps viral nuclear import and integration. In late stages of virus life cycle, LEN distorts the capsid polymer, leading to abnormal virus structure and inhibition of virus maturation.

In a phase 1 study, monotherapy with a single SC dose of LEN 450 mg suppressed plasma HIV by 2.2 log<sub>10</sub> after 9 days and maintained plasma drug concentrations antivirally active for more than 6 months [38]. These data support the potential of LEN as a long-acting agent to treat or prevent infection with HIV, and clinical studies to evaluate the efficacy and safety of LEN as a LA agent for heavily treatment-experienced and ART-naïve patients are now ongoing [41, 42].

The interim analysis of phase 2/3 randomized cohort and nonrandomized cohort trials of long-acting SC LEN in heavily treatment-experienced patients with multidrug-resistant HIV who had failed their current ARV regimen (CAPELLA trial) was presented at IAS conference on HIV science 2021 [43]. LEN (oral 600 mg dose on days 1 and 2, 300 mg on day 8, and followed by SC 927 mg injection in the abdomen on day 15 then every 6 months) combined with optimized background regimen (OBR) resulted in high rates (81%) of virologic suppression and meaningful increases by 81 cells/mm<sup>3</sup> in CD4 counts at week 26, and well tolerated with no discontinuation. Fifty-six percent of patients reported ≥1 ISR (swelling, erythema, pain, or nodule) with grade 1 severity and resolved within days. Resistance analysis though week 26 found that 4 participants among 72 participants who received SC LEN developed treatment-emergent capsid mutations. Three participants had viral rebound and resuppressed while on LEN (2 without and 1 with OBR change) and 1 participant without any fully active agent had never had viral suppression.

The interim results of phase 2 randomized, open-label, induction-maintenance study of LA SC LEN dosed every 6 months as part of a combination regimen (CALIBRATE trial) demonstrated excellent safety and efficacy of LEN for HIV treatment in ARV-naïve PLWH [44]. The trial compared SC LEN injections every 26 weeks with oral daily LEN [both in combination with tenofovir alafenamide (TAF) and FTC] or oral daily bicittegravir with TAF/FTC. High rates (92 – 100%) of viral suppression were seen in all arms; however, there was one case of drug resistance in subcutaneous LEN arm. LEN regimens led to only mild or moderate ISRs and no drug-related serious adverse events occurred.

The phase 2, randomized, open-label study to evaluate the safety and efficacy of LEN combined with ISL and two phase 2/3 trials evaluating its use as injectable PrEP are planned [45].



## CONCLUSION

The current pipeline of LA ART agents for the treatment or prevention of HIV-1 infection is reviewed. LA CAB in combination with RPV will be available soon in Korea, but many things need to be prepared for successful launch of these injectable regimen. There are also new agents and novel classes being developed and a variety of modes of administration are being studied: IM, SC, implant, patches, and microneedles. With LA ART, we can change the landscape of care and management of HIV-1 infection. LA ART will give PLWH an opportunity to relieve pill fatigue, feel freedom from anxiety of maintaining adherence, and reduce depression around social stigma. The proportion of patients choosing an LA ART will be greater than those taking a daily oral regimen in the near future.

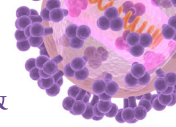
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