

HIV Prevention Utilizing Long-acting Injectables

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Pre-exposure prophylaxis (PrEP) is an essential component in ending the HIV pandemic. Unfortunately, PrEP uptake has not been optimal to date. This is due to various reasons, one of which is adherence. Long-acting injectables may help to overcome this barrier. This brief review discusses the long-acting injectables currently in use for PrEP (cabotegravir) and HIV treatment (cabotegravir and lenacapavir), as well as those currently undergoing clinical trials. Other promising agents are being studied, including islatravir and broadly neutralizing monoclonal antibodies. Furthermore, agents currently used for HIV treatment will likely be evaluated in preclinical and clinical studies for their use as PrEP agents.

Keywords

HIV, injectables, intramuscular injections, pre-exposure prophylaxis, reverse transcriptase inhibitors

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An alliance of United Nations organizations and associated partners have unified to create the United Nations Programme on HIV/AIDS (UNAIDS), which has set a goal of ending the HIV epidemic by the year 2030.¹ Similarly, the 'Ending the HIV Epidemic in the U.S.' initiative, by the Department of Human Health and Services, has an overarching goal of reducing HIV by 75% in 2025 and by 90% in 2030.² The four key strategies to attain this goal include: 'Diagnose, Treat, Prevent and Respond'. Prescription of pre-exposure prophylaxis (PrEP) medications can be a potent tool in prevention, with individuals who are adherent to daily oral PrEP experiencing almost 100% efficacy.³

Unfortunately, PrEP uptake has been limited, even in resource-rich settings, with 2020 UNAIDS targets for PrEP not met.^{4,5} Barriers to PrEP use are multifactorial and include awareness, perceived risk of HIV acquisition and access issues, among others.^{4,5} Even for those who choose PrEP, adherence to a daily oral medication can be problematic, with nonadherence potentially leading to drug resistance.^{4,5}

Long-acting preventative options should lead to an overall increase in adherence for a variety of reasons. In addition to a reduced pill burden, certain drug–drug interactions can be avoided by circumventing oral absorption. Long-acting formulations may also help improve anonymity and reduce associated stigma, due to a reduction in medication kept at the patients' residence.⁶

Many products are under evaluation, with additional agents considered for further development currently in preclinical and clinical trials. Herein, we discuss the injectable formulations currently approved by the US Food and Drug Administration (FDA) or Emergency Use Authorization and potential agents that are undergoing clinical evaluation.

Cabotegravir

In December 2021, the FDA approved cabotegravir (Apretude®; ViiV Healthcare, Research Triangle Park, NC, USA) for PrEP to reduce the risk of acquiring HIV through sexual transmission.⁷ Cabotegravir, an integrase strand transfer inhibitor, is the first long-acting preventative medication for HIV and heralds the future of HIV prevention by providing a non-daily option. For the foreseeable future, cabotegravir will likely continue to be a popular option for PrEP for an increasing number of people due to its safety profile, high potency and ability to be administered monthly or bi-monthly rather than daily.⁷

Cabotegravir is available in both oral and intramuscular (IM) formulations. It is used for both the treatment and prevention of HIV-1. As a treatment option, cabotegravir is administered in combination with the non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine, as two separate IM injections (Cabenuva®; ViiV Healthcare). As a preventative option, cabotegravir is administered as an IM injection for 1 month, then every 2 months thereafter (Apretude®).^{7,8}

The oral formulation of cabotegravir is currently used only as a 'lead-in' prior to IM administration, in order to assess tolerability. As with the other members of the integrase-inhibitor class, when administered orally, cabotegravir can interact with divalent cations via chelation. Additionally, cabotegravir is a substrate of p-glycoprotein (P-gp) and breast cancer resistant protein transporters, which may be affected by inhibitors or inducers.⁹ IM administration circumvents these potential drug–drug interactions.^{7,9}

Two traits in particular that make cabotegravir an ideal candidate as a long-acting formulation are its long half-life and antiviral potency.^{8,9} Cabotegravir's long half-life is due to its low aqueous solubility combined with a slow systemic clearance. Crystalline nanoparticles provide increased surface area compared with the oral formulation, leading to a much slower dissolution and absorption rate from the injection site and subsequently a half-life of approximately 40 days (range 25–54 days), compared with 40 hours for the oral formulation.^{10,11} Of further benefit, cabotegravir has few drug–drug interactions. Cabotegravir is metabolized by UDP glucuronosyltransferase 1A1 (UGT1A1) and is not a significant inhibitor or inducer of CYP3A enzymes.¹⁰ Only potent inducers (e.g. rifampin, carbamazepine) or inhibitors (e.g. St John's Wort) of UGT1A1 should be avoided in those taking cabotegravir.^{12,13}

Two phase III randomized controlled trials demonstrated cabotegravir's efficacy as a PrEP option.^{14–16} The HIV Prevention Trial Network (HPTN) 083 compared injectable cabotegravir with once-daily oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in cisgender men and transgender women. HPTN 084 compared injectable cabotegravir with once-daily FTC/TDF in cisgender women.^{14–16} Study participants were assigned to receive either oral FTC/TDF or cabotegravir, following a lead-in phase with oral placebo or oral cabotegravir. Cabotegravir was administered at week 5 and week 9, then every 8 weeks. The primary endpoint was incidence of HIV infection per 100 person-years. Following the initial 5-week period, study participants were followed for a total of 153 weeks for HPTN 083 and 185 weeks for HPTN 084.^{14–16}

The first large-scale clinical trial to examine a long-acting injectable (LAI), HPTN 083, showed promising results during its interim analysis (6 months) and was halted due to cabotegravir's superior efficacy.^{14,15} A total of 52 HIV infections were recorded, with 39 of these occurring in the oral FTC/TDF arm and 13 in the cabotegravir arm, resulting in a 66% lower risk of infection if the participant was taking injectable cabotegravir. Importantly, in sub-group analyses, no differences were noted with respect to age and race.

Similarly to HPTN 083, HPTN 084 was stopped at the interim endpoint analysis due to the greater efficacy seen in the cabotegravir arm.¹⁶ A total of 40 HIV infections were recorded; 36 infections occurred in the oral FTC/TDF arm, compared with four in the cabotegravir arm, resulting in an 88% lower risk of infection. Adherence was significantly higher in the cabotegravir arm. Based on the comparison of injections administered with that of expected injection visits, approximately 89% of trial participants receiving cabotegravir were adherent, whereas approximately 46% of those in the oral FTC/TDF arm were considered adherent, based on randomly sampled tenofovir concentrations. As in HPTN 083, pre-specified sub-group analyses of age, body mass index, or pregnancy showed no differences between the arms. An unblinded 1-year follow-up showed continued efficacy.^{16–18} No new HIV cases occurred in the cabotegravir arm. Additionally, pregnancy safety data showed no birth defects in 83 confirmed pregnancies from women

enrolled in HPTN 084. Women in the cabotegravir arm did discontinue cabotegravir injections until after breast-feeding stopped.¹⁷

A key issue faced by providers of cabotegravir, which likely will continue with future injectables, is reimbursement from insurance companies. Prior authorizations are often necessary, which can be time-consuming for providers and authorization is not always given, forcing patients to pay out of their own pockets. Until cabotegravir is more affordable, accessibility will be limited for many.

Lenacapavir

Lenacapavir (GS-6207) is a first-in-class capsid inhibitor, acting at multiple steps in the lifecycle of HIV, with the overall effect of inhibiting HIV-1 replication at both the early and late stages of its replication cycle.^{19,20} Additionally, lenacapavir exhibits potent antiviral effects against HIV-1, including variants with mutations associated with resistance to current antiretrovirals.²¹ At a dose of 927 mg, a single subcutaneous abdominal injection releases slowly, maintaining effective concentrations for 6 months, allowing twice-yearly maintenance injections.²² Lower doses (100 mg, 300 mg, 450 mg) produced concentrations above the 95% effective concentration for 3 months.²³

Oral and subcutaneous formulations are being evaluated in clinical trials for the treatment and prevention of HIV. Results from the phase II/III CAPELLA trial and a small phase Ib trial, both studying treatment, showed lenacapavir to be well tolerated, with few side effects.^{24,25} The most common side effect was injection-site reactions, including swelling, pain, erythema and nodules (some of which lasted several months). Transient increases in blood glucose and creatinine were observed, but no patients elected to discontinue the trial due to adverse events. Finally, drug–drug interactions are expected to be few, but specific drugs should be avoided, including potent UGT1A1 inhibitors and potent inducers of P-gp, UGT, or CYP enzymes.²⁶

Lenacapavir (Sunlenca[®]; Gilead Sciences, Inc., Foster City, CA, USA) was approved by the European Commission for the treatment of multidrug-resistant HIV-1 in August 2022.²⁷ Approval in the USA has been delayed due to manufacturing concerns regarding the borosilicate glass container vials and the vials' compatibility with lenacapavir solution. Gilead, the manufacturer of lenacapavir, re-submitted its New Drug Application to the FDA, which has accepted the application and will complete its review by December 2022.²⁸

A pair of studies are under way to examine lenacapavir as a PrEP option with twice-yearly dosing.^{29,30} Purpose-1 is an on-going clinical trial (at the time of publication) evaluating the safety and efficacy of lenacapavir in combination with emtricitabine/tenofovir alafenamide for PrEP in adolescent girls/young women at risk of HIV infection.²⁹ Purpose-2 is evaluating cisgender men, transgender women, transgender men and gender nonbinary people ≥ 16 years old who have sex with male partners (MSM).³⁰ Purpose-2 was purposefully designed by the study team to include the participation of underrepresented individuals with a goal of enrolling 50% black MSM and 20% Hispanic/Latinx MSM.³¹

Islatravir

A first-in-class nucleoside reverse transcriptase translocation inhibitor, islatravir prevents primer translocation, leading to premature chain termination.³² As with lenacapavir and cabotegravir, islatravir is considered to have high antiviral potency, having a high-binding affinity to reverse transcriptase.^{33,34}

Islatravir is being studied in oral, implant and injectable formulations.³⁴ Multiple studies are on-going for each formulation, some in combination with other antiretrovirals.³⁵ Current studies have focused on an oral formulation and a polymer implant. In animal models (rat and non-human primates), the polymer implant has provided target concentrations for up to 1 year post-implantation.³⁶

Additionally, few drug–drug interactions are expected; islatravir is not a CYP inducer or inhibitor and is eliminated via renal excretion and adenosine deaminase metabolism.³⁷ Data thus far show adverse events to be mild.

Islatravir has a high barrier to resistance.³⁸ M184V is the primary resistance mutation for islatravir, reducing antiviral susceptibility by two-fold compared with wild-type. Notably, M184V mutations have a high level of resistance to emtricitabine and lamivudine.

Two phase III studies, IMPOWER 22 and IMPOWER 24, are evaluating once-monthly oral islatravir for PrEP.^{39,40} The study population of IMPOWER 22 is cisgender women, while that of IMPOWER 24 is cisgender men and transgender women who have sex with men.^{39,40} A phase I study (MK-8591-034) is intended to evaluate the injectable formulation.³⁵ At the time of writing, several clinical studies have been placed on full clinical, or partial clinical hold by the FDA due to safety concerns regarding a decline in both total lymphocyte and CD4 counts in certain study subjects. Most studies are resuming at a lower dose of islatravir.³⁵

Broadly neutralizing antibodies

VRC01LS and VRC07-523LS are two long-acting broadly neutralizing monoclonal antibodies (bNAbs) undergoing studies to evaluate their safety and efficacy. bNAbs are rare antibodies found in some people who spontaneously control HIV. bNAbs have unique properties, particularly the ability to neutralize a broad spectrum of different HIV envelopes.⁴¹ Several hundred bNAbs have been identified and are being studied as therapeutic monoclonal antibodies in the prevention and suppression of HIV infection. Two examples that are undergoing studies for use as PrEP are VRC01LS and VRC07-523LS.⁴² Both of these have incorporated the lysine–serine (LS) mutation, which significantly extends their half-life.

VRC01LS

The HVTN 704/HPTN 085 and HVTN 703/HPTN 081 studies were conducted to evaluate whether VRC01, a bNAb, could prevent HIV infection. While the study determined that VRC01 did not prevent overall HIV-1 acquisition compared with placebo, it did provide data for proof of concept.⁴³ VRC01LS has an increased binding affinity to the neonatal Fc receptor, due to two amino acid changes, which extends its serum half-life compared with VRC01.

An open-label, phase I, dose-escalation study included healthy adults without HIV aged 18–50 years.⁴² Three groups received single doses of VRC01LS intravenously at doses of 5 mg/kg, 20 mg/kg and 40 mg/kg, while one group received a single subcutaneous dose at 5 mg/kg. Two additional groups received three administrations 12 weeks apart at doses of 5 mg/kg subcutaneously and 20 mg/kg intravenously, respectively. Overall, there were no serious adverse events and VRC01LS was determined to be safe and well tolerated. The study confirmed that the serum half-life of VRC01LS was four times longer than the wild-type VRC01 at 71 days and it retained its activity through the duration of the 48-week study, with no antibodies being detected. Furthermore, the intravenous administrations resulted in higher peak serum concentrations than

subcutaneous administration; however, serum concentrations at week four were similar between both administration types.⁴²

VRC07-523LS

VRC07-523LS targets the CD4 binding site of the HIV-1 envelope protein, as a manufactured variant of VRC01. Healthy adults aged 18–50 years without HIV received either a single dose of 1 mg/kg, 5 mg/kg, 20 mg/kg or 40 mg/kg intravenously, or three doses of either 20 mg/kg or 5 mg/kg subcutaneously at 12 week intervals in a phase I open-label study.⁴⁵ Study results reported that VRC07-523LS was safe and well tolerated, with only mild-to-moderate side effects; malaise and myalgia were most common with intravenous administration, while pain and tenderness were most common with subcutaneous administration.⁴⁴

VRC07-523LS was also studied in the CAPRISA 012A phase I study, which evaluated two doses of VRC07-523LS and/or PGT121 when administered subcutaneously.⁴⁵ PGT121 targets the V3 glycan-dependent epitope region of the HIV envelope protein. The CAPRISA 012A study included 45 females aged 18–40 years and at low risk for HIV infection. Nine groups received one of the following regimens: VRC07-523LS 5 mg/kg one dose, VRC07-523LS 10 mg/kg one dose, VRC07-523LS 5 mg/kg repeat dose at 12 weeks, VRC07-523LS 10 mg/kg repeat dose at 24 weeks, PGT121 3 mg/kg one dose, PGT121 3 mg/kg repeat dose at 12 weeks, VRC07-523LS + PGT121 5mg/kg + 3 mg/kg one dose, PGT121 10 mg/kg one dose, or VRC07-523LS 20 mg/kg one dose. Overall, both VRC07-523LS and PGT121 were well tolerated, with injection site tenderness and headaches being the most commonly reported adverse events, which were mild in severity. The antibodies maintained their neutralizing activity. It was determined that further studies with VRC07-523LS, in combination with other bNAbs, would be of interest.⁴⁵

VM-1500A

VM-1500A, a next-generation NNRTI, has recently shown unique pharmacokinetic properties that have increased interest in the development of a LAI formulation for HIV treatment. The prodrug form of VM-1500A, elsulfavirine (Eplida®; Viroim Inc., San Diego, CA, USA), is currently approved for the treatment of HIV/AIDS in its N-acyl sulphonamide form.⁴⁶ With a half-life of approximately 8 days, VM-1500A presents a new opportunity to facilitate adherence and potentially improve long-term outcomes.⁴⁷

A single-centre study in Russia evaluated VM-1500A-LAI in volunteers who were not infected with HIV as part of the first-in-human, open-label, phase I study.⁴⁸ Subjects received single ascending doses of 150 mg, 300 mg, 600 mg and 1200 mg once monthly, in addition to two doses of 600 mg monthly IM after a 2-week daily run-in of its prodrug, elsulfavirine oral capsules. Overall, the results of the pharmacokinetic profile observed were consistent with sustained delivery. Additionally, the dose of 600 mg/mL, split into two simultaneous injections, supported the therapeutic trough concentration.⁴⁸

Thirty-six participants were enrolled in a phase I/II study to evaluate VM-1500A in patients infected with HIV who transferred from previous stable therapy (NNRTI +2NRTIs).⁴⁹ Participants were randomized to receive differing doses of VM-1500A: 1200 mg monthly, 1200 mg followed by 900 mg monthly, or 1200 mg followed by 600 mg monthly.⁴⁹ The study is complete; however, results have not yet been posted.

A phase II/III study plans to evaluate VM-1500A plus two NRTIs from the first-line standard-of-care therapy by randomizing subjects into three

treatment groups.⁵⁰ Subjects will receive either LAI 600 (elsulfavirine + VM-1500A-LAI 600 mg), LAI 900 (elsulfavirine+VM-1500A-LAI 900 mg), or standard-of-care therapy. The study intends to enroll 438 participants and be completed in October 2023.⁵⁰

Summary

Though the advent of LAIs has taken decades of research to realize, a variety of options are now, or soon to be, available. In addition to injectables (subcutaneous and intravenous), implants, patches and long-acting oral products are also being studied. Long-acting formulations are poised to improve adherence for certain patients and patient populations, which is essential for effective therapy.⁵¹ Persons with cognitive dysfunction, psychiatric disorders or certain physical impairments may benefit from a treatment that does not require daily oral administration.

Despite the optimism surrounding LAIs, some potential drawbacks exist. Some patients are injection-adverse, others are unable, or unwilling,

to attend regular clinic visits (e.g. due to financial constraints and employment responsibilities). Additionally, availability to some at-risk populations remains a problematic barrier.

One concern from a pharmacokinetic standpoint is the 'pharmacokinetic tail' of long-acting formulations; this is the waning concentrations, which can fall below the effective inhibitory concentrations necessary for HIV suppression, when patients are no longer taking the medication (e.g. due to non-adherence or stopping PrEP). Concentrations below the effective inhibitory concentrations can potentially lead to drug resistance. Cross-resistance can occur, rendering a class unusable for treatment. Cost is another hurdle that must be addressed. The problems associated with cabotegravir, as discussed above, will continue with any new formulations. Finally, although initial data for cabotegravir in pregnant women are encouraging, far more data are needed for all the injectables under study, with regard to pregnancy and breastfeeding. □

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