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## A New Era in the Treatment and Prevention of HIV Infection is Brought about by Long-Acting Antiretrovirals



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### ABSTRACT

The FDA, EMA, and Health Canada have just approved the combination of Cabotegravir and Rilpivirine, which is a long-acting antiretroviral. HIV patients' therapy is going to undergo a revolutionary change thanks to this innovative drug delivery method, which will reduce the daily pill burden to just six intramuscular injections annually. Furthermore, the first-in-class nucleoside reverse transcriptase translocation inhibitor is Isatravir is meant to be administered as an implant with a minimum one-year dose interval. Currently, patients receiving long-acting antiretroviral treatments (LA-ARTs) are administered these drugs at predetermined standard doses regardless of their weight or body mass index (BMI), and host genetic and non-genetic characteristics that may impact their systemic disposition are not taken into account. In addition to discussing their implications, especially from a clinical pharmacokinetics perspective, for the future management and prevention of HIV infection issues that will remain crucial in the absence of a cure or reliable vaccine—the current review attempts to bring the state of knowledge on these novel, promising LA-ARTs up to date.



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## INTRODUCTION

HIV stands for human immunodeficiency virus. It is a virus that attacks the immune system, the body's defence against infection. HIV can lead to AIDS, which is acquired immunodeficiency syndrome. AIDS is the most advanced stage of HIV infection. HIV is transmitted through contact with infected blood, semen, or vaginal fluids. This can happen through sexual intercourse, sharing needles or syringes, or receiving blood transfusions. HIV can also be transmitted from mother to child during pregnancy, childbirth, or breastfeeding. Once a person is infected with HIV, the virus attacks and destroys a type of white blood cell called a CD4 cell. CD4 cells are essential for the immune system to function properly<sup>i,ii</sup>. As the number of CD4 cells decreases, the person becomes more susceptible to infection. There have been several improvements made to HIV infection care since the advent of highly active ART approximately 20 years ago. These include the reduction of complicated regimens to single fixed-dose combination tablets and an increase in both efficacy and tolerability<sup>iii</sup>. ART continues to be the cornerstone of HIV treatment and prevention in the absence of a cure or a reliable vaccine. A powerful HIV integrase strand transfer inhibitor (INSTI) (dolutegravir, bictegravir) or an NNRTI (rilpivirine, doravirine, etravirine) is combined with two NRTIs (tenofovir, emtricitabine, lamivudine) in the current oral triple-drug treatment of HIV infection. Recently, simpler combinations of dual therapies have demonstrated the same efficacy as traditional triple therapy. The creation of long-acting formulations, which currently guarantee two months of effective plasma concentrations, is a potential strategy to overcome the resistance. The creation of new antiretroviral medications is probably going to result in an extension of this dose interval in the near future. In addition to preventing drug use, long-acting antiretroviral therapy (LA-ART) will enhance patient privacy and lessen social stigmas related to HIV. Up to 70% of eligible patients interested in starting long-acting injectable ART (LAI-ART) value the convenience, freedom, secrecy, and emotional benefits of not having to continually remind themselves of their HIV status through daily tablet use. Extending the period between injections will increase LAI-ART interest and reduce injection discomfort.<sup>iv,v</sup>

## CABENUVA

CABENUVA is a comprehensive prescription regimen used to treat HIV-1 infection in patients 12 years of age and older who weigh at least 77 lbs (35 kg). It can be used to replace an existing HIV-1 medication regimen. When a patient's healthcare practitioner determines

they meet specific conditions. To treat HIV, a prescription drug called Cabenuva is administered in isolation without the use of any other antiviral medications.<sup>vi,vii</sup>

## CAUTION

- Those who have previously experienced hypersensitivity responses to rilpivirine, cabotegravir, or any of the injection kit's inactive ingredients shouldn't receive it.
- Inform your doctor of all the medications you take now, as well as any that you begin or stop taking. Numerous medications may interact with one another, and some medications may make Cabenuva less effective and shouldn't be taken together.
- There have been serious injection-related reactions with the rilpivirine component. If you notice any severe pain, swelling, or redness at the injection site, let your doctor know.
- Injections of rilpivirine and cabotegravir have been associated with adverse liver toxicity; therefore, your doctor will need to keep an eye on your liver function tests.
- There have also been reports of depression. Inform your physician if your mood shifts in any way.
- It is crucial that a new regimen be started no later than one month after the last injection if you stop taking Cabenuva or if virological failure is suspected, even though residual concentrations of cabotegravir or rilpivirine may linger in your system for up to 12 months after your last injections.

Your doctor must ascertain that you are able to tolerate the active ingredients, cabotegravir and rilpivirine, prior to administering Cabenuva injections. You will start taking tablets of cabotegravir and rilpivirine once a day with food, at least 28 days before to your first injection. Using these medications together safely will be determined in part by this "lead-in dose".

Both rilpivirine and cabotegravir are supplied as individual single-dose vials in the Cabenuva injection kit. Two distinct kit strengths exist. In addition, two vial adapters, two syringes, two syringe labels, and two intramuscular injection needles (23-gauge, 1½ inch) are included in each dosage set. Natural rubber latex is not used to make the vial stoppers.

Cabenuva 400/600mg kit

- One single-dose vial of cabotegravir extended-release injectable suspension 400 mg/2 mL (200 mg/mL).
- One single-dose vial of rilpivirine extended-release injectable suspension 600 mg/2 mL (300 mg/mL).

Cabenuva 600/900mg kit

- One single-dose vial of cabotegravir extended-release injectable suspension 600 mg/3 mL (200 mg/mL).
- One single-dose vial of rilpivirine extended-release injectable suspension 900 mg/3 mL (300 mg/mL).

## **LENACAPAVIR**

The U.S. Food and Drug Administration (FDA) has approved the prescription medication lenacapavir, also known by the brand name Sunlenca, for the treatment of HIV infection in people who have previously received therapy, have developed drug resistance, and who fulfill specific requirements as established by a healthcare professional. Lenacapavir is always taken with other anti-HIV medications<sup>viii,ix</sup>.

## **CAUTION**

Tell your healthcare provider the following before taking lenacapavir:

- if lenacapavir or any other medication allergies you may have.
- if you use medications that have a high potential to stimulate CYP3A. Lenacapavir's effectiveness may be lowered by these medications.
- if you suffer from any further illnesses.
- in the event that you are or intend to get pregnant. See your doctor about the advantages and disadvantages of taking lenacapavir while pregnant.
- Whether you are nursing a child or intend to nurse one. The Guideline advises discussing breastfeeding alternatives with your healthcare professional if you are an HIV positive person living in the United States. Less than 1% of women with suppressed viral loads can pass HIV to their unborn child through breast milk.

- If you are utilizing birth control that is hormone-based (via tablets, implants, or vaginal rings). See the HIV info HIV and Birth Control infographic for additional details on using birth control and HIV medications concurrently.
- About any additional medications, including prescription and over-the-counter, vitamins, dietary supplements, and herbal remedies, including St. John's wort, that you currently use or intend to take. Lenacapavir may have an impact on how other medications or goods function, and other medications or goods may have an impact on how lenacapavir functions. When lenacapavir is used with specific medications or goods, major adverse consequences may occur.

## CONCLUSION

Injectable versions of drugs with high potency and lengthy  $t_{1/2}$  (e.g., cabotegravir and rilpivirine) are becoming widely used. The LAI cabotegravir/rilpivirine formulation can maintain effective plasma concentrations for 2 months, potentially transforming HIV management in the future. New antiretroviral medicines are expected to lengthen the current dose interval. Further characterization of possible concerns with the extended PK profile is necessary to guarantee safe and effective treatment for all patients. I development is a viable option for improving HIV therapy and prevention. Implant-based contraception is likely to be widely accepted. However, more advances are essential. Further research on LA-ARTs can improve their efficacy, tolerability, long-term safety, overcoming DDIs, and pharmacogenetic traits, while also considering patient preferences and convenience. TDM is leading the way in personalized treatment and prevention to better address the requirements of patients. LA-ARTs will transform HIV therapy and prevention. However, these treatments have only been tested in clinical studies, which do not reflect the unique circumstances of many PLWH. To effectively treat and prevent HIV, it's important to closely monitor people on LA-ART. This includes monitoring viral suppression and CD4 count, as well as measuring antiretroviral medication levels in plasma, tissues, and cellular compartments. More research is needed to fully realize the therapeutic and preventive potential of LA-ARTs for HIV infection in real-life settings.<sup>x</sup>

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