



# What's on the Horizon for Long-Acting Pre-Exposure Prophylaxis (PrEP)?

Successfully ending the HIV epidemic will require the use of multiple prevention tools. Previous studies have shown that using once-a-day oral Truvada as PrEP to prevent HIV does not fit into everyone's life. Although once-daily oral PrEP is 99.9% effective at preventing HIV, research shows that some people who try it struggle with adherence. Poor adherence to PrEP increases the chances of the medication being ineffective in preventing HIV, which can result in a person getting HIV. Researchers are now developing new long-acting medication or medication that does not have to be taken daily to prevent HIV. By developing additional options to prevent HIV, more populations will now have increased opportunities to take advantage of more simplified ways to prevent HIV.

Communities broadly can expect some new and innovative medications to enter the field to prevent HIV. The HIV Prevention Trials Network (HPTN) researched the use of long-acting cabotegravir (CAB LA) to prevent HIV. HPTN 083 was the first large-scale clinical trial of a long-acting injectable drug with the potential to be used for HIV prevention. The study examined whether a long-acting form of the anti-HIV drug cabotegravir injected once every eight weeks could safely protect cisgender men and transgender women who have sex with men from getting HIV infection at least as well as Truvada. CAB LA proved superior to Truvada in preventing HIV infection, and this was confirmed in a separate study, HPTN 084, that compared the efficacy of the two drugs in cisgender women.<sup>1</sup>

Along with long-acting cabotegravir, other long-acting PrEP agents are being studied. Merck is currently leading a clinical trial on an experimental drug called islatravir. Islatravir belongs to a group of HIV drugs called nucleoside reverse transcriptase translocation inhibitors (NRTTIs).<sup>2</sup> Previous studies showed that islatravir is highly potent and stays in the body longer than most drugs; because of this, it can be taken once weekly for treatment or once monthly—or even less often—for PrEP.<sup>3</sup>

There are ongoing studies for islatravir; one study is being led by Merck and the Bill & Melinda Gates Foundation. IMPOWER 22 is evaluating the safety

and efficacy of islatravir PrEP in cisgender women and adolescent girls at high risk for HIV in sub-Saharan Africa. The study will enroll 4,500 participants who will be assigned to receive once-monthly oral islatravir or once-daily Truvada (tenofovir disoproxil fumarate/emtricitabine).

Another planned trial, IMPOWER-024, will enroll cisgender men and transgender women who have sex with men in countries around the world. They will be randomized to receive once-monthly islatravir or once-daily Truvada or Descovy (tenofovir disoproxil fumarate/raltegravir), the latter of which is not yet approved for people exposed to HIV via vaginal sex.<sup>4</sup>

An implantable formulation of islatravir is also being studied for PrEP. The implant, similar in size to a matchstick, releases a small amount of the drug over time, much like implants used for long-acting contraception. An early study of HIV-negative volunteers showed that the implant released enough drug to prevent HIV for a year.

Gilead is studying an experimental drug called lenacapavir as long-acting PrEP. Originally, lenacapavir was only being studied as a drug to treat HIV; however, Gilead announced the exciting addition of a new study arm to their Women's HIV Prevention Study evaluating the use of lenacapavir as an injectable PrEP option administered every six months.<sup>5</sup> An additional lenacapavir for PrEP study in men who have sex with men and persons of trans and non-binary experience (PURPOSE 2) is underway, with a projected trial completion date of early 2024.<sup>6</sup>

Lenacapavir belongs to a group of HIV drugs called capsid inhibitors. Capsid inhibitors interfere with HIV capsid, a protein shell that protects HIV's genetic material and enzymes needed for replication. Capsid inhibitors can disrupt HIV capsid during multiple stages of the viral life cycle. When used as treatment, this prevents HIV from multiplying and reduces the amount of HIV in the body. In the prevention context, the hope is that lenacapavir will be able to block the acquisition of HIV infection.

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<sup>1</sup> Jefferys R. PrEP and Microbicides Pipeline Report 2021. New York: Treatment Action Group; 2021. [https://www.treatmentactiongroup.org/wp-content/uploads/2021/07/pipeline\\_2021\\_hiv\\_PrEP\\_final.pdf](https://www.treatmentactiongroup.org/wp-content/uploads/2021/07/pipeline_2021_hiv_PrEP_final.pdf)

<sup>2</sup> Markowitz M, Sarafianos SG. EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine, MK-8591): a novel HIV-1 reverse transcriptase translocation inhibitor. *Curr Opin HIV AIDS*. 2018;13(4):294–9. doi:10.1097/COH.0000000000000467

<sup>3</sup> Highleyman L. "Islatravir shows promise for once-monthly oral PrEP." *POZ Magazine*. 2021 January 26. <https://www.poz.com/article/islatravir-shows-promise-oncemonthly-oral-prep>

<sup>4</sup> ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). Oral islatravir (MK-8591) once-monthly as preexposure prophylaxis (PrEP) in men and transgender women who have sex with men and are at high risk for HIV-1 infection (MK-8591-024) (Impower-024); 2020 December 3. <https://www.clinicaltrials.gov/ct2/show/NCT04652700>

<sup>5</sup> Gilead Sciences (Press Release). Gilead announces new arm of HIV Women's Prevention Study to evaluate the investigational long-acting HIV-1 capsid inhibitor lenacapavir in addition to Descovy for PrEP. 2020 December 21. <https://www.gilead.com/news-and-press/company-statements/gilead-announces-new-arm-of-hiv-womens-prevention-study>

<sup>6</sup> ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). Study to assess the effectiveness and safety of lenacapavir for human immunodeficiency virus (HIV) pre-exposure prophylaxis (PURPOSE 2); 2021 June 14. <https://clinicaltrials.gov/ct2/show/NCT04925752>