# Apretude Approved—the First Long-Acting Injectable PrEP Option

Every-other-month cabotegravir injections may work even better than daily pills for HIV prevention.

December 20, 2021 By Liz Highleyman

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On December 20, the Food and Drug Administration (FDA) approved Apretude, or extended-release cabotegravir, as the first long-acting injectable option for HIV pre-exposure prophylaxis (PrEP). Apretude, which is administered by a health care worker every other month, is indicated for adults and adolescents weighing at least 77 pounds to reduce the risk of sexually acquired HIV.

"Today's approval adds an important tool in the effort to end the HIV epidemic by providing the first option to prevent HIV that does not involve taking a daily pill," Debra Birnkrant, MD, director of the Division of Antivirals in the FDA's Center for Drug Evaluation and Research, said in a press release. "This injection, given every two months, will be critical to addressing the HIV epidemic in the U.S., including helping high-risk individuals and certain groups where adherence to daily medication has been a major challenge or not a realistic option."

Cabotegravir is a long-acting integrase inhibitor from ViiV Healthcare. People who wish to use Apretude will first receive two intramuscular injections in the buttocks administered one month apart, and then every two months thereafter. Another option is for people to take oral cabotegravir (Vocabria) for four weeks to determine how well they tolerate the drug. Every-other-month injections can be given within a seven-day window before or after the scheduled dose. If a person misses an injection by more than a week, they can substitute daily cabotegravir pills for up to two months.

In contrast, the Truvada (tenofovir disoproxil fumarate/emtricitabine and generic equivalents) PrEP pill must be taken daily on an ongoing basis or "on demand" before and after sex (also known as PrEP 2-1-1). Descovy (tenofovir alafenamide/emtricitabine) is taken once daily.

Apretude is approved for cisgender and transgender men and women with no limitations based on the type of sex they have. Truvada is also approved for everyone, but Descovy PrEP is not approved for cisgender women or other people exposed to HIV via vaginal sex because clinical trials did not include this population. Although Apretude trials did not include trans men, they are still eligible to use the injections.

Two large trials showed that Apretude works even better than PrEP pills. The HPTN 083 trial (NCT02720094) enrolled more than 4,000 cisgender men and transgender women who have sex with men in the United States, Latin America, Asia and Africa. About half of U.S. participants were Black men, the group with the highest rate of new HIV diagnoses. They were randomly assigned to receive cabotegravir injections every two months or once-daily Truvada.

The study was halted ahead of schedule in May 2020 after an interim analysis showed that Apretude worked as well as daily pills. Further results, published in The New England Journal of Medicine, showed that the injections were 66% more effective at preventing HIV acquisition. Ongoing follow-up showed that the injections reduced the risk of HIV by 69% compared with Truvada. This is a remarkable finding, given that daily Truvada itself reduces the risk of HIV by about 99% for gay and bisexual men who use it consistently.

A parallel study, HPTN 084 (NCT03164564), compared Apretude versus daily Truvada for more than 3,000 mostly young cisgender women in sub-Saharan Africa. This trial was also stopped early after an interim analysis found that the injections were more effective.

Researchers first reported that women randomly assigned to receive the injections had an 89% lower risk of acquiring HIV compared with those who used daily pills. Further follow-up, presented at this year's International AIDS Society Conference on HIV Science, showed that cabotegravir was even more effective—92%—after reclassifying a participant who was found to already have HIV when she started the study.

Apretude is currently being studied in adolescents. So far, safety data appear comparable to that of the adult trials.

In both of the adult trials, Apretude was safe and well tolerated. The most common side effect is injection site reactions, including pain, redness or swelling. These are usually mild or moderate and last only a few days. While most trial participants reported such reactions, few stopped the injections for this reason. In other studies, most people who tried both PrEP pills and the injections said they preferred the latter.

The Apretude prescribing information includes precautions about rare but potentially serious adverse effects, including hypersensitivity reactions, hepatotoxicity (liver damage) and depression.

Apretude should only be used by people who do not already have HIV. The prescribing information includes a warning to not use it without a confirmed negative HIV test immediately prior to starting the drug. In addition, an HIV test should be repeated before each injection. If a person with HIV uses Apretude, this can lead to the emergence of drug-resistant virus. People who test positive for HIV while using Apretude for PrEP must transition to a complete combination HIV treatment regimen.

Cabotegravir is also a component of Cabenuva (cabotegravir/rilpivirine), the only complete long-acting injectable regimen for HIV treatment.

According to the Centers for Disease Control and Prevention (CDC), only about 25% of the 1.2 million people who could benefit from PrEP have received a prescription for it. In anticipation of Apretude's approval, it is included in the CDC's updated PrEP guidelines, which were released earlier this month.

The greater effectiveness of Apretude compared with PrEP pills appears to be attributable to better adherence. Daily or on-demand oral PrEP requires a high level of adherence, which some individuals find difficult to achieve. What's more, some people prefer not to think about HIV every day, do not want to have pill bottles that could reveal they are at risk or may have concerns about their pills being lost or stolen.

"Many people who are vulnerable to HIV have complex lives that can make taking a daily pill to prevent HIV a burden," Gabriel Maldonado, executive director and CEO of TruEvolution, said in a ViiV press release. "This can include stigma, fears about accidental disclosure of their medicine, as well as general complications from daily living. Together, these issues may contribute to low rates of PrEP usage and the expansion of the HIV epidemic. Our community has been in dire need of additional HIV prevention options that may address their evolving needs, and cabotegravir long-acting for PrEP represents an exciting new option to help them reduce their risk of acquiring HIV."

On the other hand, because Apretude is administered by a health care provider, it requires six clinic visits a year. This may impose an additional burden on HIV providers, especially in the context of reduced services due to COVID-19.

One Apretude injection costs $3,700, about as much as two months' worth of daily Truvada of Descovy pills, but substantially more than generic tenofovir disoproxil fumarate/emtricitabine. It is not yet clear whether the federal rule that requires most insurers to cover PrEP pills will also apply to the injections. ViiV has not said whether it plans to offer co-pay or patient assistance programs.

Different people have different needs and preferences, and experts stress the importance of having more prevention options so individuals can choose the one that works best for them. The availability of this new injectable option will hopefully lead to greater PrEP uptake among people at risk for HIV.

"Psychologically, PrEP offers an HIV negative person a sense of agency over their HIV status, and a way to enjoy sex without fear," Damon Jacobs, founder of the PrEP Facts Facebook group, told POZ. "Injectable PrEP offers a new option for people to feel proactive, responsible, and empowered about their sexual pleasure and protection."

Click here for more news about PrEP.

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