Twice-Yearly Lenacapavir PrEP Prevents HIV in Women

Cisgender women who received injections every six months had zero new HIV infections in a large clinical trial.

June 21, 2024 By Liz Highleyman

The twice-yearly HIV capsid inhibitor lenacapavir demonstrated 100% efficacy for preventing acquisition of the virus in a large study of young cisgender women in Africa, Gilead Sciences announced yesterday.

The PURPOSE 1 trial showed that lenacapavir pre-exposure prophylaxis (PrEP), administered by subcutaneous injection once every six months, significantly reduced HIV incidence compared with the background rate and was superior to daily oral Truvada (tenofovir disoproxil fumarate/emtricitabine, or TDF/FTC). There were no new infections among women assigned to lenacapavir versus 16 among those who received Truvada.

“Lenacapavir is highly potent, can last for six months, removes the numerous challenges of daily adherence and can be given discreetly and privately, which really sets it up as the kind of PrEP agent that would fit into a lot of people’s lives,” Jared Baeten, MD, PhD, Gilead’s vice president of HIV clinical development, told POZ. “More than 2,000 women were randomized to receive lenacapavir, and none of them acquired HIV. That has never been seen before in a Phase III trial of any HIV prevention intervention.”

Based on these interim findings, the trial’s independent data monitoring committee recommended that the blinded part of the study should be stopped and lenacapavir should be offered to all participants on an open-label basis. Gilead indicated that further results will be presented at a future scientific conference—perhaps AIDS 2024 this summer in Munich.

Multiple Studies Underway

PrEP was first approved more than a decade ago, but it has still not reached its full potential. While urban white gay and bisexual men eagerly adopted PrEP, uptake has been slower for other groups, including women and Black and Latino men who have sex with men. The Centers for Disease Control and Prevention estimates that only about a third of the 1.2 million people who could benefit from PrEP are using it.

While oral PrEP is very effective, additional options are still needed. Some people have trouble remembering to take a pill every day, some don't want to constantly be reminded about HIV and some are hesitant to have pill bottles that could be lost or stolen or reveal that they are at risk for HIV. Experts say having multiple PrEP options to choose from helps ensure that everyone can find a method that works for them.

https://t.co/CqDZe1kX3n Zero HIV infection among >2000 young women aged 16-25 years in Uganda and South Africa using 6 monthly Lenacapavir subcut injections for Pre exposure prophylaxis. This is just amazing and exhilarating! Our climb out of this epidemic is more feasible!

— Linda-Gail Bekker (@LindaGailBekker) June 21, 2024

"Twice-yearly lenacapavir for PrEP, if approved, could provide a critical new choice for HIV prevention that fits into the lives of many people who could benefit from PrEP around the world—especially cisgender women," Linda-Gail Bekker, MBChB, PhD, of the Desmond Tutu HIV Center at the University of Cape Town in South Africa, said in Gilead's press release. "While we know traditional HIV prevention options are highly effective when taken as prescribed, twice-yearly lenacapavir for PrEP could help address the stigma and discrimination some people may face when taking or storing oral PrEP pills as well as potentially help increase PrEP adherence and persistence given its twice-yearly dosing schedule."

The Food and Drug Administration (FDA) approved Gilead's Truvada as the first once-daily oral PrEP option in July 2012. It is indicated for all adults and adolescents at risk for HIV, but there has been lingering concern about how well oral PrEP works for cisgender women. In 2019, the FDA gave the nod to a second PrEP option, Gilead's Descovy (tenofovir alafenamide/emtricitabine, or TAF/FTC), for certain populations. In 2021, the agency approved ViiV Healthcare's Apretude (cabotegravir), which is administered by a health care provider every other month, as the first long-acting injectable PrEP option. An ultra-long-acting formulation of cabotegravir that could potentially be administered once every four months is in development.

Lenacapavir's long half-life in the body extends the PrEP dosing interval to once every six months. The drug disrupts HIV's capsid, the cone-shaped shell that surrounds the viral genetic material and essential enzymes. Like other antiretrovirals, lenacapavir stops HIV replication—it is not a vaccine

that trains the immune system to fight the virus. (After four decades of effort, there are still no effective HIV vaccines.) But twice-yearly administration brings PrEP closer to, say, a flu or COVID vaccine in terms of implementation.

In 2022, the FDA approved lenacapavir (sold as Sunlenca) for the treatment of people with multidrug-resistant HIV. But while a single antiretroviral is adequate for HIV prevention, treatment requires a combination regimen, and lenacapavir currently has no partner drugs that can be taken at such a long interval.

PURPOSE 1 is one of five ongoing or planned trials of lenacapavir for PrEP. The studies are comparing the rate of HIV infection among people who use lenacapavir or oral PrEP against the known background rate among people in the same population who don't use PrEP. Now that oral and injectable PrEP are proven effective and widely available, it would be unethical to compare new experimental prevention methods against a placebo.

When the FDA approved Descovy for PrEP, the indication excluded people who are at risk for acquiring HIV from vaginal sex due to a lack of clinical trial data for cisgender women, transgender men and nonbinary people with vaginas. But Gilead did not make the same mistake again, including all relevant populations in its lenacapavir PrEP studies.

PURPOSE 1 (NCT04994509) enrolled more than 5,300 young cisgender women ages 16 to 25 in South Africa and Uganda, countries with high HIV incidence among women. PURPOSE 2 (NCT04925752) enrolled more than 3,000 cisgender and transgender men, trans women and nonbinary people who have sex with men in the United States, Argentina, Brazil, Mexico, Peru, South Africa and Thailand.

The two Phase III trials are running in parallel, but PURPOSE 1 happened to have its initial data read-out sooner because it completed enrollment faster, according to Baeten. PURPOSE 2 results are expected in late 2024 or early 2025. These pivotal trials are evaluating the safety and efficacy of lenacapavir and oral PrEP, and their results will support applications for regulatory approval.

Two other smaller Phase II studies, PURPOSE 3 (NCT06101329) and PURPOSE 4 (NCT06101342), are evaluating lenacapavir and TDF/FTC for cisgender women disproportionately affected by HIV and people who inject drugs in the United States. These trials are designed to assess the safety, pharmacokinetics and acceptability of lenacapavir and oral PrEP in these populations, but they are not powered to assess efficacy. Finally, PURPOSE 5 is evaluating lenacapavir and TDF/FTC in Europe, focusing on populations that are often underrepresented in clinical trials.

PURPOSE 1 Results

PURPOSE 1 is actually two studies in one, evaluating both lenacapavir and Descovy. Thus, it helps fill the data gap that has held up approval of Descovy PrEP for cisgender women. Three groups were randomly assigned to receive lenacapavir, Descovy or Truvada in a 2:2:1 ratio. Lenacapavir and Descovy were separately compared against the background HIV incidence rate and Truvada.

In the interim results, there were zero new infections among the 2,134 women who received lenacapavir, 16 new infections among the 1,068 participants assigned to Truvada and 39 new infections among the 2,136 women who received Descovy. The corresponding HIV incidence rates were 0.00, 1.69 and 2.02 per 100 person-years, respectively. Meanwhile, the background HIV incidence rate was 2.41 per 100 person-years.

The study therefore met its primary efficacy endpoint of demonstrating the statistical superiority of lenacapavir over the background incidence rate as well as the secondary endpoint of lenacapavir over Truvada, according to Gilead's announcement.

Descovy, on the other hand, did not provide statistically superior protection compared with the background incidence rate. Gilead described the incidence rates for Descovy and Truvada as "numerically similar." Baeten cautioned that the confidence intervals were wide in this comparison, meaning there was considerable uncertainty. Previous studies of oral PrEP for cisgender women have found challenges with adherence to daily pills, and this may be the problem here as well. Adherence analyses, including measurement of tenofovir levels in blood samples, are currently underway, he said.

All three PrEP methods were generally well tolerated, and no new safety concerns were identified. Gilead's announcement did not include details about side effects, but in studies of lenacapavir for HIV treatment, the most common adverse reactions were nausea and injection site reactions, such as pain, redness, swelling and nodules.

Clinicians and advocates generally lauded the study results—with some calling it a game changer—but others expressed concerns.

One advantage of lenacapavir for PrEP is that it is currently not widely used for HIV treatment, so if someone has a breakthrough infection and develops drug resistance, it would not limit their treatment options as much as resistance to cabotegravir and other integrase inhibitors.

One downside of lenacapavir is that it is a moderate inhibitor of CYP3A, an enzyme that processes many drugs, meaning it could lead to drug-drug interactions for up to nine months after the last dose. Lenacapavir could potentially raise levels of fentanyl, oxycodone, erectile dysfunction medications, steroids and statins. What's more, other drugs known as CYP3A inducers (such as some tuberculosis medications) could potentially decrease lenacapavir levels, making it less effective.

"A generally younger population [on PrEP] is likely to be on fewer meds than people on HIV treatment, but there are some real areas of concern, including recreational and chemsex drugs and drugs like Viagra," Laura Waters, MD, of the Central and North West London NHS Foundation Trust, told POZ. "I don't want to be the rain on an exciting parade, and benefits will outweigh any small harms, but it's an important thing to communicate."

But the biggest concern is that lenacapavir PrEP, if approved, might not be accessible to the

people who need it most. This is already the case for Apretude, which was shown to be more effective than daily oral PrEP for both gay men and cisgender women but so far is not widely used. Lenacapavir for HIV treatment is priced at around $3,000 per month, while generic versions of Truvada can cost as little as $30 per month.

“There is no time to waste if we are to translate these exciting clinical trial results into actual public health impact and expand the toolbox of HIV prevention choices,” AVAC executive director Mitchell Warren said in a statement. “[T]here is urgent work to be done now by communities, policy makers, funders and program implementers to design and build HIV prevention programs and prepare health systems to deliver the growing array of biomedical PrEP options, including the addition of twice-yearly injectable lenacapavir.”

“Since oral PrEP was first shown to be safe and effective 14 years ago, the global health community has failed in delivering PrEP at scale and with equity, and we have, therefore, not seen the impact that we need,” he continued. “The lessons from the past are clear, and we now must act on them and move with speed, scale and urgency. There can be no excuses and no delays.”

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