Twice-Yearly Lenacapavir PrEP Highly Effective in Second Study

New results for gay men and gender-diverse people confirm stellar HIV prevention findings for women reported this summer.

September 12, 2024 By Liz Highleyman

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Twice-yearly lenacapavir reduced the risk of HIV acquisition by 96% in a large study of gay and bisexual men and transgender and nonbinary people in seven countries, Gilead Sciences announced on September 12.

The Phase III PURPOSE 2 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 just two new infections among trial participants assigned to receive lenacapavir.

#GileadNews: We've announced topline results from an interim analysis of our second Phase 3 clinical trial of our investigational medication for #HIV prevention. This continues to confirm the medication's potential to help those who need or want PrEP. https://t.co/doqLFMzqMg pic.twitter.com/oTsT4s43BH

— Gilead Sciences (@GileadSciences) September 12, 2024

These long-awaited findings confirm results from the PURPOSE 1 trial, presented at the International AIDS Conference in July, which showed that lenacapavir PrEP was 100% effective for young cisgender women in Africa. Oral PrEP is around 99% effective when taken consistently, but several studies have found that injectable antiretrovirals can encourage better adherence.

The PURPOSE 2 news "is just terrific and really means the labelling can be inclusive of just about all populations who could benefit from this wonderful prevention innovation," said PURPOSE 1 lead investigator Linda-Gail Bekker, MBChB, PhD, of the Desmond Tutu HIV Center at the University of Cape Town. "Oral PrEP still remains a terrific option for those who prefer it and can use it, but for those who have struggled, this is just amazing. We remain very excited about seeing regulatory and generic company engagement happening urgently now so people can benefit as soon as possible."

Even before today's data readout, advocates were putting pressure on Gilead to ensure that lenacapavir PrEP is available to those who need it once it's approved.

"It is extremely exciting to hear that the study showed favorable results. I think this will add an additional option of choice that will really empower key communities," Daniel Driffin, DrPH, MPH, of the HIV Vaccines Trials Network told POZ after his remarks at the U.S. Conference on HIV/AIDS, taking place this week in New Orleans. "The conversation should already be started on what a successful rollout will look like, especially for Black and brown communities, folks across the South and folks on Medicaid and Medicare."

PURPOSE 2 Findings

PrEP was first approved in 2012, but it has still not reached its full potential. 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 highly effective, additional options are still needed. Some people, for example, may have trouble remembering to take a pill every day or may be hesitant to have pill bottles that could be lost or stolen or reveal that they are at risk for HIV. Currently, ViiV Healthcare's Apretude (injectable cabotegravir), which is administered every other month, is the longest-acting PrEP option. Having multiple choices helps ensure that everyone can find a prevention method that works for them.

"The difficulty some people can experience with taking an oral pill every day, including challenges with adherence and stigma, have hindered uptake and persistence of the standard of care for too long, thus blunting PrEP's impact on HIV prevention," PURPOSE 2 principal investigator Onyema Ogbuagu, MBBCh, of Yale School of Medicine, said in a Gilead news release. "This breakthrough

adds significantly to our arsenal of tools to move us closer to achieving an AIDS-free generation."

In 2022, the Food and Drug Administration (FDA) approved lenacapavir (sold as Sunlenca), the first HIV capsid inhibitor, for the treatment of people with multidrug-resistant HIV. Lenacapavir currently has no equally long-acting partner drugs to make up a complete treatment regimen, but a single antiretroviral is adequate for HIV prevention. While lenacapavir is not a vaccine that trains the immune system to fight the virus, twice-yearly PrEP would be a game-changer.

PURPOSE 2 (NCT04925752) enrolled more than 3,000 cisgender and transgender men, trans women and nonbinary people who have sex with men at more than 80 sites in the United States, Argentina, Brazil, Mexico, Peru, South Africa and Thailand. They were randomly assigned in a 2:1 ratio to receive either lenacapavir or once-daily Truvada pills. Now that oral and injectable PrEP are proven effective, it would be unethical to compare new experimental prevention methods against a placebo.

There were two new HIV diagnoses among the 2,180 participants in the lenacapavir group—meaning 99.9% remained HIV-free—compared with nine cases among the 1,087 people assigned to Truvada, according to Gilead. The HIV incidence rates were 0.10 versus 2.37 per 100 person-years, respectively. Lenacapavir reduced the risk of HIV acquisition by 96% relative to the background incidence among people not on PrEP and by 89% relative to daily Truvada.

Lenacapavir and Truvada were both generally safe and well-tolerated with no new safety concerns. Gilead's announcement did not include details about side effects, but in studies of lenacapavir for HIV treatment, the most common drug-related adverse events were nausea and injection site reactions. Lenacapavir injections form a long-lasting depot in the fat layer of the abdomen that slowly releases the drug over time, which can sometimes be felt as a nodule under the skin.

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.

[Update October 7, 2024: PURPOSE 2 principal investigator Colleen Kelley, MD, MPH, of Emory University, presented further details at the HIV Research for Prevention Conference (HIVR4P 2024) in Lima, Peru.

The most common adverse events (which were not necessarily directly related to lenacapavir or Truvada) were sexually transmitted infection. Serious adverse events occurred in 3.3% of people in the lenacapavir group and 4.0% of those in the Truvada group. The most common injection site reactions among lenacapavir recipients were nodules (63%), pain (56%) and redness (17%), which decreased with subsequent injections over time. Fewer than 1% (26 people) discontinued lenacapavir due to such reactions. People who received Truvada saw a greater decline in kidney function than those in the lenacapavir group (eGFR -2.9 versus +0.6, respectively, at 52 weeks). Kelley noted that researchers are now analyzing detailed data from the two lenacapavir recipients

who seroconverted, including pharmacokinetics and resistance.

Another presentation detailed the diverse demographics of study participants. More than 20% were “gender-diverse,” including 15% transgender women, 1% transgender men and 6% nonbinary people. The study enrolled participants as young as 16; about a third were ages 25 or younger. Participants were enrolled in South Africa (59%), Mexico (47%), Argentina (34%), Brazil (31%), Peru (30%), the United States (19%) and Thailand (11%). More than a third (38%) were Black, 13% were Asian and 15% were “other”; 63% were of Latino ethnicity.

“These data reinforce that twice-yearly lenacapavir could be a highly effective and potentially game-changing HIV prevention choice that we have long hoped for in our efforts to end the HIV epidemic,” Kelley said in a second news release. “PURPOSE 2 was intentionally designed to reflect the lives and locations of many people who are disproportionately affected by HIV around the world by focusing on gender, racial, ethnic and geographic diversity.”]

[Update November 29, 2024: Further PURPOSE 2 data were presented at the HIV Drug Therapy congress in Glasgow on November 13, and full study results were published in The New England Journal of Medicine on November 27, 2024.]

[Update December 19, 2024: Gilead announced that it has completed New Drug Application submissions to the Food and Drug Administration seeking approval of twice-yearly lenacapavir PrEP based on the results of PURPOSE 1 and PURPOSE 2.]

[Update: On June 18, 2025, twice-yearly lenacapavir, brand name Yeztugo, was approved by the Food and Drug Administration for prevention of sexually acquired HIV.]

Ensuring Access

Gilead plans to submit the data from PURPOSE 1 and PURPOSE 2 to the FDA for a prevention indication by the end of the year, which could support the initial launch of the first twice-yearly HIV PrEP option in 2025. Two smaller Phase II studies, PURPOSE 3 and PURPOSE 4, are evaluating lenacapavir and TDF/FTC PrEP for cisgender women and people who use drugs in the United States, while PURPOSE 5 is evaluating lenacapavir and TDF/FTC in Europe.

“Now that we have a comprehensive dataset across multiple study populations, Gilead will work urgently with regulatory, government, public health and community partners to ensure that, if approved, we can deliver twice-yearly lenacapavir for PrEP worldwide for all those who want or need PrEP,” said Gilead chairman and CEO Daniel O’Day. The company said it is “committed to making lenacapavir available in the countries where the need is greatest, including expediting voluntary licensing partners to supply high-quality, low-cost versions of lenacapavir.”

Advocates and researchers lauded the new findings but expressed concerns about cost and access. Lenacapavir for HIV treatment costs around $4,000 per month—although that is not expected to be its price for prevention—while generic versions of TDF/FTC can cost as little as $20 per month. A study presented at the International AIDS Conference showed that the price of lenacapavir could be brought down to around $40 per year with voluntary licensing and

competition between generic suppliers. The Affordable Care Act requires insurers to cover PrEP at no cost, but coverage of injectable PrEP has so far been inconsistent.

“This is the second impressive result for this new HIV prevention option, opening up more possibilities for choice for even more people to find an option that is right for them,” AVAC executive director Mitchell Warren said in a statement. “Beyond expanded choice, a twice-yearly injection has the potential to transform the way we deliver HIV prevention to people who need and want it most—from an easier to follow regimen for individuals to a decreased burden on healthcare systems that are stretched to the limit. But these data only matter if the field moves with speed, scale and equity.”

[Update October 4, 2024: Gilead announced that it will work with pharmaceutical manufacturers to produce and sell generic lenacapavir for PrEP in 120 resource-limited countries with high HIV incidence rates.]

“The results of PURPOSE2 extend the impressive evidence base that lenacapavir is safe and highly effective as PrEP, with the potential for profound impacts on those people who remain susceptible to HIV acquisition,” National Institute of Allergy and Infectious Diseases director Jeanne Marrazzo, MD, MPH, told POZ. “The challenge for the field is not only access and scale up with keen cost considerations, but committing to pursuing other prevention interventions so that policymakers and individuals have access to the widest array of choice in the event of barriers—including viral resistance, cost and access.”

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http://beta.docker.poz.com/article/twiceyearly-lenacapavir-prep-highly-effective-second-study