Once-Yearly Lenacapavir Looks Promising for HIV PrEP

Two longer-lasting formulations produce drug concentrations even higher than those of highly effective twice-yearly lenacapavir.

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Twice-yearly lenacapavir pre-exposure prophylaxis (PrEP), which is expected to launch this summer, has been hailed as a major breakthrough, but once-yearly HIV prevention shots could have an even bigger impact on the epidemic.

Gilead Sciences revealed in December that it is working on new formulations of the injectable antiretroviral that could potentially be administered just once a year. Researchers reported the first Phase I data this week at the Conference on Retroviruses and Opportunistic Infections (CROI 2025) and in The Lancet. The company considers the results promising enough to skip directly to Phase III trials.

“Once-yearly intramuscular lenacapavir for PrEP has the potential to improve PrEP uptake and persistence and thus improve the scalability and public health impact of PrEP in populations who would benefit most,” Renu Singh, PhD, Gilead’s senior director of clinical pharmacology, and colleagues concluded.

Daily oral PrEP is highly effective when taken consistently, but other options are still needed. Some people may have trouble remembering to take a pill every day, may feel stigma around using antiretrovirals that also treat HIV or may be hesitant to have pill bottles that could be lost or stolen. Lenacapavir is an antiretroviral drug that blocks HIV replication—not a vaccine that trains the immune system to fight the virus. But all traditional HIV vaccine candidates tested in large trials have failed, so long-acting PrEP is the next best thing.

Lenacapavir (Sunlenca), the first HIV capsid inhibitor, was approved in 2022 but only as part of a combination treatment regimen for people with multidrug-resistant virus. It has a long half-life in the body that allows for infrequent administration. The injections form a “depot” under the skin that releases the drug slowly over time. “As you go higher in concentration, the release is slower, and when the release is slower, it can last longer,” Singh said at a CROI media briefing.

Commenting on the study, HIV researcher and clinician Joseph Eron, MD, of the University of North Carolina at Chapel Hill, noted that the once-yearly formulation does not require any special

technology, which will make it easier for generic companies to manufacture the compound for use in low-income countries.

A pair of Phase III trials showed that twice-yearly lenacapavir is highly effective for HIV prevention. Results from the PURPOSE 1 trial showed that lenacapavir PrEP was 100% effective for young cisgender women in Africa—significantly more so than daily Truvada (tenofovir disoproxil fumarate/emtricitabine) pills. Findings from PURPOSE 2 showed that lenacapavir injections every six months reduced the risk of HIV acquisition by 96% relative to background incidence and by 89% compared to Truvada for gay and bisexual men and gender-diverse people in the United States and six other countries. In both trials, the injections were safe and generally well-tolerated.

Given its impressive efficacy as twice-yearly PrEP, Singh's team evaluated the pharmacokinetics, safety and tolerability of two different once-yearly formulations of lenacapavir.

This Phase I trial enrolled 40 healthy adults with a low likelihood of HIV acquisition. About two thirds were men, 80% were white, 20% were Black and most were of Latino ethnicity. The median age was approximately 35 years. The median body mass index (BMI) was within the overweight range; people with Class 2 obesity (a BMI over 35) were excluded.

The participants received a single 5,000 milligram dose of lenacapavir, given as two 5 milliliter intramuscular injections in the buttocks at the same time. In contrast, twice-yearly lenacapavir is administered as a single subcutaneous injection into the fat layer beneath the skin of the abdomen.

Half of the study participants received a formulation containing 5% ethanol, which reduces the viscosity of the injection, while the other received a 10% ethanol formulation. Pharmacokinetic samples were collected at days 5, 10 and 15 and then every 100 days through 56 weeks.

Lenacapavir plasma concentrations remained above the 95% effective concentration for at least 56 weeks with both formulations. Drug levels increased rapidly after administration, reaching a maximum concentration in 12 weeks for the first formulation and 10 weeks for the second formulation, and then slowly and steadily declined.

The highest median concentrations of once-yearly lenacapavir (247.0 nanograms per milliliter for the first formulation 336.0 ng/ml for the second formulation) remained well above the median peak concentration of twice-yearly lenacapavir (67.3 ng/ml). The median trough, or lowest, concentrations at week 52 were 57.0 ng/ml and 65.5 ng/ml, respectively, again exceeding the median trough concentration of twice-yearly lenacapavir (23.4 ng/ml) in PURPOSE 1 and PURPOSE 2. The median area under the curve—a measure of total drug exposure over time—was also higher with both once-yearly formulations compared with twice-yearly lenacapavir. What's more, there were no outliers with especially low drug levels, and everyone had concentrations similar to or higher than those of twice-yearly lenacapavir at the end of the study.

Adverse events were mostly mild to moderate with both formulations, according to Singh. The most common side effect was injection site pain, reported by 80% of people who received the first

formulation and 75% of those who received the second formulation. This was generally mild, resolved within a week and was reduced by applying an ice pack prior to the injection. Nodules under the skin where the drug depot is deposited are a common side effect of subcutaneous injections but were not reported with the intramuscular formulations. No severe drug-related adverse events were observed with either formulation.

Eron noted that 5 ml is about a teaspoon, and he said he was “surprised people tolerate it that well, but it’s great that they did.” Given that the concentrations were so high, Singh suggested that the final dose would probably end up being less than 5 ml.

“As a clinical pharmacologist, it gives me great pleasure to see a small molecule last this long—it has never been done before. And, overall, these results indicate that once-yearly lenacapavir has the potential to provide similarly high efficacy as twice-yearly subcutaneous lenacapavir, which is huge.”

Gilead plans to start a Phase III trial of once-yearly lenacapavir PrEP in the second half of this year, bypassing intermediate Phase II trials. Phase III studies provide the data needed for Food and Drug Administration approval. Data from the trial might be ready for review in 2027.

Once-yearly lenacapavir could potentially also be used for HIV treatment, but it would need to be combined with other medications to maintain viral suppression, and nothing with such a long duration is on the horizon. “Finding another molecule—whether it’s an antibody or a small molecule—that will last a year is a challenge,” Eron said.

While these results are groundbreaking, researchers, advocates and global health officials stress that the promise of long-acting PrEP can be realized only if it is widely available and affordable to everyone who needs it. Gilead announced last year that it will work with pharmaceutical manufacturers to provide generic lenacapavir for PrEP in more than 100 resource-limited countries with high HIV incidence. But access is a growing concern given recent cuts to U.S. foreign aid programs, including PEPFAR (the President’s Emergency Plan for AIDS Relief), the main distributor of PrEP worldwide.

“Gilead is continuing to innovate in our work to develop additional person-centered long-acting injectable and oral options to help people find an HIV prevention choice that is right for them,” said Jared Baeten, MD, PhD, Gilead’s senior vice president for clinical development and virology therapeutic area head, in a news release. “Once-yearly lenacapavir, if approved, could become an important new HIV prevention option that could help address PrEP adherence and persistence challenges for individuals who need or want PrEP around the world.”

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