Next Steps for Longer-Acting PrEP

Once-yearly injectable PrEP and once-monthly prevention pills are now in late-stage trials.

April 13, 2026 By Liz Highleyman

Twice-yearly injectable lenacapavir (Yeztugo) has been hailed as a breakthrough in HIV prevention, but a once-yearly formulation could have an even greater impact on the epidemic. And for people who prefer pills, once-monthly MK-8527 pre-exposure prophylaxis (PrEP) could be an option. Researchers provided updates on these longer-acting PrEP options—both now in Phase III trials—at this year's Conference on Retroviruses and Opportunistic Infections (CROI 2026).

Once-Yearly Lenacapavir

A pair of Phase III trials showed that twice-yearly lenacapavir is highly effective for HIV prevention. In PURPOSE 1, subcutaneous injections administered every six months were 100% effective at preventing HIV among young cisgender women in Africa. In PURPOSE 2, the shots reduced the risk of HIV acquisition by 96% relative to background incidence 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.

At last year's CROI and in The Lancet, researchers from Gilead Sciences reported results from a Phase I study showing that two longer-lasting intramuscular formulations of lenacapavir yielded drug concentrations even higher than those of twice-yearly injections. Injection site reactions were generally mild and transient, and the intramuscular shots did not produce nodules under the skin like the subcutaneous shots. Gilead considered the results promising enough to skip directly to Phase III.

This year, Gilead scientists reported on a model-informed drug development approach for the dose selection and design of a Phase III trial of once-yearly lenacapavir PrEP.

The researchers developed a population pharmacokinetic model using data from four Phase I trials that included a total of 151 participants with more than 3,000 lenacapavir concentration measurements. Based on the large and diverse populations in PURPOSE 1 and PURPOSE 2, they assessed various oral loading doses and intramuscular injection doses, aiming to select a regimen that would maintain protective lenacapavir concentrations for at least 52 weeks.

The simulations predicted that an intramuscular dose of 3,000 milligrams would yield a 52-

week trough concentration (lowest level between doses) exceeding the observed 26-week trough in PURPOSE 1 and 2. This dose was also projected to maintain a median lenacapavir concentration more than fourfold higher than the inhibitory level for at least a year. An oral loading dose (600 mg on days 1 and 2) would be needed to rapidly achieve the desired concentration, as is the case for the approved twice-yearly regimen.

“Leveraging the totality of clinical and nonclinical data generated to date, we developed a model-informed drug development strategy to determine the appropriate dose and to support the efficacy of lenacapavir as pre-exposure prophylaxis when administered intramuscularly once yearly without a large efficacy-powered Phase III study,” the researchers concluded.

The Phase III PURPOSE 365 trial (NCT07047716) is now recruiting a diverse population of 300 cisgender and transgender men and women and nonbinary people ages 16 and older who are sexually active and considered to be at risk for HIV. (Those currently using twice-yearly lenacapavir PrEP are ineligible.) Participants in this single-arm, open-label study will receive 600 mg oral lenacapavir for two days and 3,000 mg lenacapavir administered as two injections in the upper buttocks once yearly. The study is expected to conclude in the fall of 2028.

Monthly Oral PrEP

MK-8527 is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI). It works differently than the familiar nucleoside reverse transcriptase inhibitors, both stopping translocation (movement of the reverse transcriptase enzyme) and acting as a defective building block as HIV copies its RNA to DNA.

Merck previously explored its first NRTTI candidate, islatravir, for long-acting HIV treatment and prevention, but clinical trials were placed on hold after some participants experienced decreased CD4 T-cell or total lymphocyte counts at high doses. Treatment trials resumed using a lower dose, but development of islatravir as a monthly PrEP option was halted.

Fortunately, MK-8527 does not share the same safety concerns. Following promising preclinical studies (published in PLOS Biology), Merck scientists reported at CROI 2024 that the drug showed good antiviral activity in HIV-positive people and reached protective levels in HIV-negative volunteers with no notable safety signals in Phase I studies.

A Phase II trial tested the safety and pharmacokinetics of MK-8527 for once-monthly oral PrEP in 350 adults with a low likelihood of HIV exposure in the United States, Israel and South Africa. They were randomly assigned to receive MK-8527 at doses of 3, 6 or 12 mg or a placebo every four weeks for up to six months. As reported at last summer’s International AIDS Society Conference on HIV Science, MK-8527 was well tolerated across doses with no meaningful changes in mean CD4 or total lymphocyte counts. In the 6 mg and 12 mg dose groups, drug concentrations were maintained above the threshold for protection for more than 28 days. No one acquired HIV during the study.

At this year's CROI, Merck researchers reported on dose selection for Phase III trials of MK-8527. Here, too, they used a population pharmacokinetic modeling approach, leveraging cumulative data from more than 400 participants in five Phase I studies and the Phase II study. They found that an 11 mg dose was predicted to be generally well tolerated and maintain drug concentrations above the preventive efficacy threshold. This dose reached an effective level within an hour, provided coverage for the whole month after the first dose and had a seven-day dosing window. What's more, this dose was projected to provide protective drug levels throughout pregnancy and to be effective and well tolerated for adolescents weighing at least 77 pounds.

Two Phase III trials using the 11 mg dose are now underway. EXPrESSIVE-10 (NCT07071623) aims to enroll nearly 4,600 sexually active young women and adolescent girls in Kenya, South Africa and Uganda, while EXPrESSIVE-11 (NCT07044297) will enroll about 4,400 sexually active people who could benefit from PrEP—including gay men, transgender women and men and nonbinary people—in 16 countries. In both trials, participants will be randomly assigned to receive once-monthly MK-8527 or standard daily PrEP pills (tenofovir disoproxil fumarate/emtricitabine).

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