Weekly Oral HIV Treatment Looks Good at Two Years

A once-weekly combination of lenacapavir and islatravir pills maintained viral suppression for 96 weeks.

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A once-weekly oral regimen combining the HIV capsid inhibitor lenacapavir and the experimental nucleoside reverse transcriptase translocation inhibitor islatravir maintained viral suppression for two years, according to study results presented at the European AIDS Conference (EACS 2025) in Paris.

The latest Phase II trial data showed that most people who switched from a widely used once-daily oral regimen to weekly lenacapavir and islatravir pills maintained an undetectable viral load at 96 weeks. If the findings are confirmed in ongoing Phase III studies, this could become the longest-acting antiretroviral regimen that doesn't involve injections.

Once-daily HIV regimens are highly effective, but some people have trouble taking pills every day. While long-acting injectables are the answer for some, others find it inconvenient to schedule injection appointments—or they simply don't like shots.

Lenacapavir, from Gilead Sciences, works differently than other antiretrovirals, so it remains active against HIV that has developed extensive drug resistance. A twice-yearly injectable formulation, sold as Sunlenca, was approved in 2022 as part of a combination regimen for people with multidrug-resistant HIV. Long-acting lenacapavir alone, sold as Yeztugo, was recently approved for pre-exposure prophylaxis (PrEP). Lenacapavir also comes in a pill form, which is used as part of the initial loading dose and may be used for temporary "bridging" if an injection must be missed.

Islatravir (MK-8591), from Merck, is a first-in-class nucleoside reverse transcriptase translocation inhibitor, which interferes with the enzyme in a different way than the familiar nucleoside/nucleotide reverse transcriptase inhibitors. A once-daily regimen of islatravir plus doravirine (Pifeltro) is effective for previously untreated people and maintains viral suppression in those who switch from another regimen, but the drug's long half-life in the body makes it a candidate for longer-acting treatment.

The development of islatravir hit a snag in 2021 when participants in early trials experienced a

decline in CD4 T-cell or total lymphocyte counts, but further analysis revealed that the doses used in these studies were too high. Clinical trials of islatravir plus doravirine and islatravir plus lenacapavir therefore resumed using a lower dose.

Amy Colson, MD, MPH, research director at the Community Resource Initiative in Boston, presented the latest findings from a Phase II trial (NCT05052996) evaluating once-weekly oral lenacapavir plus islatravir as a switch option for people currently on once-daily Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine) with viral suppression.

The study enrolled 104 adults with an undetectable viral load (less than 50 copies), no history of virological failure, a CD4 count of at least 350 (median 755) and an adequate total lymphocyte count. The median age was 40 years, about 80% were men and the study population was 48% white, 40% Black, 25% Latino and 6% Asian or Native American. The participants were randomly assigned to either stay on Biktarvy or switch to lenacapavir (300 milligrams) and islatravir (2 mg) pills taken once a week.

At last year's IDWeek meeting, Colson reported that 94.2% of the 52 participants who switched to lenacapavir plus islatravir maintained viral suppression at 48 weeks, as did 92.3% of those who stayed on Biktarvy.

[Update: Week 24 and Week 48 results were published in Annals of Internal Medicine on December 23, 2025.]

This year, she presented data for 46 people on the experimental combination who entered an extension phase of the study and were followed for at least 96 weeks. Of the initial 52 participants, two discontinued the weekly regimen due to adverse events unrelated to the study drugs, two stopped for personal reasons and two decided not to enter the extension phase.

After two years on treatment, 88.5% of participants initially assigned to lenacapavir plus islatravir and 100% of those who completed the extension phase maintained viral suppression. No one had a viral load of 50 or higher at 96 weeks or at the time of study discontinuation, and no emergent viral resistance to lenacapavir or islatravir was detected. Adherence, as measured by pill counts, exceeded 99%.

The combination was safe and well tolerated. Through 96 weeks, 19.2% of participants taking lenacapavir plus islatravir experienced treatment-related adverse events, all mild to moderate. The most common side effects were dry mouth and nausea. There was no clinically significant decline in CD4 count (mean decrease of 33 cells) or total lymphocyte count, and no one discontinued treatment for this reason. Weight and body mass index remained stable over the two years of follow-up.

In a related poster at the conference, Joseph Eron, MD, of the University of North Carolina at Chapel Hill, and colleagues described patient-reported outcomes in the same trial.

Participants who switched to weekly lenacapavir plus islatravir and those who stayed on daily

Biktarvy both reported overall health scores. Satisfaction scores in the lenacapavir plus islatravir group increased at four weeks and remained stable thereafter, while scores in the Biktarvy group were unchanged from baseline. More people taking lenacapavir plus islatravir reported that the regimen fit conveniently into their lifestyle. What's more, about two thirds of those who switched said their prior daily regimen was more burdensome and they were more satisfied with the weekly regimen.

The latest study findings support the continued development of lenacapavir and islatravir as a once-weekly oral regimen for people with viral suppression. A fixed-dose combination pill containing the two drugs is being tested as a switch option in the Phase III ISLEND-1 (NCT06630286) and ISLEND-2 (NCT06630299) trials. ISLEND-1 is for people on Biktarvy at baseline, while ISLEND-2 includes people on any guideline-recommended daily oral regimen. Enrollment is now complete, and initial results are expected next Spring.

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