Weekly Islatravir/Lenacapavir Combo Pill Maintains Viral Suppression

If approved, the new single-tablet regimen would be the first oral treatment option that does not require daily pills.

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A once-weekly single-tablet regimen containing islatravir and lenacapavir maintained viral suppression in people with HIV who switched from standard daily oral treatment, according to two studies presented yesterday at the 26th International AIDS Conference (AIDS 2026) in Rio de Janeiro.

Modern antiretroviral therapy is highly effective and generally well tolerated, so the choice of a regimen often comes down to ease of use, and medications that can be taken less frequently are the future of HIV treatment. While long-acting injectables are the answer for some people, others find it inconvenient to schedule injection appointments—or they simply don't want shots.

"Single-tablet regimens have transformed the outlook for millions of people living with HIV," said Amy Colson, MD, MPH, of Community Resource Initiative and Cambridge Health Alliance, in a news release. "Having a treatment option with once-weekly dosing can expand choice to help address individual needs and preferences."

Islatravir, from Merck, is the first nucleoside reverse transcriptase translocation inhibitor, which interferes with the HIV enzyme in a different way than familiar nucleoside/nucleotide reverse transcriptase inhibitors. A once-daily pill combining islatravir and Merck's nucleoside/nucleotide reverse transcriptase inhibitor doravirine, sold as Idvynso, was approved in April.

Development of islatravir hit a snag in late 2021 when some people in earlier trials saw a decline in their CD4 T-cell or total lymphocyte counts. But scientists determined that the doses used in those studies were too high. After a clinical hold by the Food and Drug Administration, trials resumed using lower doses that do not cause this side effect.

Lenacapavir, from Gilead Sciences, is the first HIV capsid inhibitor. A twice-yearly injectable formulation, sold as Sunlenca, was approved in 2022 as a component of combination therapy for people with multidrug-resistant HIV. Injectable lenacapavir alone, sold as Yeztugo, was approved for pre-exposure prophylaxis (PrEP) in June 2025. Lenacapavir also comes in a pill form, which is used as part of an initial loading dose before injections.

A Phase II clinical trial tested islatravir and lenacapavir taken as separate pills as a switch option for people with an undetectable viral load on Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine). Researchers previously reported that the experimental combination regimen maintained viral suppression at 24 weeks, 48 weeks and 96 weeks.

This set the stage for the Phase III ISLEND-1 and ISLEND-2 trials, which tested a combination pill containing 2 milligrams of islatravir and 300 mg of lenacapavir. In June, Merck and Gilead announced top-line findings from these trials, showing that the islatravir/lenacapavir single-tablet regimen is safe and effective at 48 weeks. At AIDS 2026, Jürgen Rockstroh, MD, of University Hospital Bonn in Germany, presented detailed results from ISLEND-1, and Colson presented findings from ISLEND-2. The studies will continue through 96 weeks.

ISLEND-1

The randomized, double-blind ISLEND-1 trial (NCT06630286) enrolled 607 participants with viral suppression on Biktarvy at more than 100 sites in the United States and 10 other countries in North and South America, Europe and Asia.

The median age was approximately 49 years; half were older than 50, and 17% were older than 65%, reflecting the contemporary HIV population, Rockstroh noted. Nearly 80% were cisgender men, about 20% were cisgender women and 2% were transgender, gender-nonconforming or nonbinary. About 45% were white, about 30% were Black, 11% were Asian and a quarter identified as Latino.

The participants had a viral load below 50 for at least six months and no history of virological failure. At baseline, the median CD4 T-cell count was high, at approximately 740. The participants did not have hepatitis B, and about 80% had evidence of hepatitis B virus (HBV) immunity. This is important because neither islatravir nor lenacapavir has activity against HBV, unlike the tenofovir alafenamide in Biktarvy. Participants were strongly encouraged to get vaccinated against hepatitis B if not already immune, Rockstroh said.

The study participants were randomly assigned to switch to the islatravir/lenacapavir combination pill or stay on Biktarvy.

The results, published simultaneously in The New England Journal of Medicine, show that islatravir/lenacapavir is noninferior to Biktarvy, meeting the study's primary endpoint, Rockstroh reported. Adherence was very good in both groups, at 98.9% and 95.5%, respectively. However, more people in the islatravir/lenacapavir group achieved at least 90% adherence (97.7% vs 89.4).

At 48 weeks, 93.4% of people who switched to the new combination pill and 92.4% of those who stayed on Biktarvy maintained viral suppression below 50 copies. No one on the combination pill and one person on Biktarvy (0.3%) had a viral load of 50 or higher. No emergent resistance to islatravir or lenacapavir was detected.

Treatment was safe and generally well tolerated; 13% in both groups experienced treatment-

related adverse events. The most frequently reported side effects were nausea and headache, but these were uncommon in both groups (3%). Two participants on the combination and none on Biktarvy reported dizziness. In both groups, only 2% stopped study treatment due to adverse events. There was one treatment-related serious adverse event in the islatravir/lenacapavir group (a grade 3 skin rash), and one unvaccinated person discontinued treatment due to hepatitis B. Body weight did not change in either group.

Importantly, people taking islatravir/lenacapavir did not experience white blood cell decreases like those seen in the earlier discontinued trials using higher doses of islatravir. CD4 counts remained stable in both groups, and both saw a similar small increase in total lymphocyte counts.

During the discussion of the findings, Annie Luetkemeyer, MD, of the University of California San Francisco—who presented results from a study of another once-weekly oral combination further back in the pipeline (islatravir plus ulonivirine)—noted that while the 2 mg dose of islatravir in both coformulations is about 10 times higher than the 0.25 mg dose in the recently approved daily doravirine/islatravir combination pill, it is 10 times lower than the weekly dose used in the halted studies.

ISLEND-2

The open-label ISLEND-2 trial (NCT06630299) enrolled 626 people with viral suppression on various standard-of-care daily oral combinations in 13 countries; unlike ISLEND-1, it included sites in South Africa. The study population was generally similar. The median age was 52 years, two thirds were men, 42% were white, 31% were Black, 19% were Asian and 20% were Latino.

At study entry, nearly 90% were taking a single-tablet regimen. Most (76%) were on a combination that included an integrase inhibitor, 15% were on a non-nucleoside reverse transcriptase inhibitor regimen and 8% were on a protease inhibitor regimen. Again, they had a viral load below 50 for at least six months, no history of virological failure and did not have hepatitis B. The median baseline CD4 count was a bit higher (mean 778).

The participants were randomized to switch to the islatravir/lenacapavir combination pill or stay on their current treatment.

Here, too, islatravir/lenacapavir was non-inferior to standard therapy, Colson reported. At 48 weeks, 95.2% of people who switched to the new coformulation and 95.5% of those who stayed on their existing regimen maintained viral suppression. One person who switched to islatravir/lenacapavir (0.3%) and four people who did not change their treatment (1.3%) had a viral load of 50 or higher. No emergent resistance to islatravir or lenacapavir was detected.

Again, treatment was safe and well tolerated; 18% of people on islatravir/lenacapavir experienced treatment-related adverse events compared to less than 1% in the unchanged treatment group, but none were severe. The most common adverse events in the islatravir/lenacapavir group were headache (5%), diarrhea (3%) and nausea (3%). Two people on the new combination pill and one on a continued daily regimen stopped study treatment due to adverse events. Body weight stayed

about the same, and CD4 and total lymphocyte counts remained stable in both groups.

ISLEND-2 also looked at patient-reported outcomes. Among those who switched, nearly two thirds said their previous daily regimen was more burdensome, only 1% said the same about the weekly islatravir/lenacapavir pill and about 30% said the burden was similar. At 48 weeks, more than 75% said they were more or much more satisfied with the weekly treatment, 14% were equally satisfied and about 3% preferred their prior daily treatment. Adherence approached 100% in both groups.

Asked why there would be a need for both islatravir/lenacapavir and islatravir/ulonivirine, which Merck is also developing as a single-tablet regimen, Luetkemeyer said that having more options is better for patients. Rockstroh added that if both weekly coformulations are approved, there would be more competition, which could lower cost and improve access.

“Treatment needs to fit into people’s lives, not the other way around,” said incoming International AIDS Society president Kenneth Ngure, PhD, MPH, of Jomo Kenyatta University of Agriculture and Technology, in a news release. “People living with HIV need new treatment options that offer flexibility, and a weekly pill could broaden the choices available for adults with virological suppression.”

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