Islatravir Plus Ulonivirine Shows Promise as Weekly Oral Regimen

After separate pills maintained viral suppression, Merck will test a combination pill containing the two novel antiretrovirals.

July 30, 2026 By Liz Highleyman

An experimental antiretroviral regimen containing islatravir and ulonivirine shows promise as a weekly oral treatment option, according to a study presented yesterday at the 26th International AIDS Conference (AIDS 2026) in Rio de Janeiro.

Daily antiretroviral treatment is usually highly effective, but some people have trouble taking a pill every day. Oral medications that can be taken once a week could help relieve "pill fatigue" and improve adherence for those who don't want to use long-acting injectables.

"Once-weekly antiretroviral therapy is an attractive option for many people living with HIV to potentially improve adherence over daily regimens," said presenter Annie Luetkemeyer, MD, of the University of California San Francisco.

Merck's islatravir 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 doravirine, sold as Idvynso, was approved in April.

Development of islatravir hit a roadblock in 2021 after some people in earlier HIV treatment and prevention trials experienced 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.

Ulonivirine (formerly MK-8507) is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against HIV strains that have developed resistance to older drugs in its class.

At the 2024 International AIDS Society Conference on HIV Science, researchers reported that a once-weekly regimen of islatravir at higher doses plus ulonivirine maintained viral suppression in people who switched from once-daily Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine). Some participants saw drops in their CD4 and total lymphocyte counts, however, and this trial was

halted. Ulonivirine was not implicated in the white blood cell declines.

After determining that the tested doses of islatravir were too high, Merck went on to design a new Phase II study testing a lower 2 milligram dose of islatravir plus 200 mg ulonivirine (NCT06891066). Luetkemeyer noted that while the 2 mg islatravir dose in both this regimen and an experimental islatravir/lenacapavir coformulation (also presented at AIDS 2026) is about ten times higher than the 0.25 mg dose in the daily Idvynso pill, it is ten times lower than the weekly dose used in earlier halted studies.

This randomized open-label trial enrolled 157 participants at more than 20 sites in the United States, Australia and Switzerland. The median age was 48 years, nearly three quarters were men, 55% were white, 32% were Black, 6% were Asian and 24% identified as Latino.

At study entry, they were on Biktarvy with a viral load below 50 for at least six months. They had no history of treatment failure and no known ulonivirine resistance mutations. The median CD4 count was high, at 810. People with active hepatitis B or hepatitis C were excluded, but about a quarter lacked evidence of hepatitis B virus (HBV) immunity due to prior infection or vaccination.

This is important because neither islatravir nor ulonivirine is active against HBV, unlike the tenofovir alafenamide in Biktarvy. Luetkemeyer said that excluding unvaccinated people would have been a “real missed opportunity,” and the investigators encourage participants to get the hepatitis B vaccine if they were not already immune.

The study participants were randomly assigned to switch to once-weekly islatravir plus ulonivirine—a regimen consisting of four pills—or stay on Biktarvy. Luetkemeyer presented results from the primary endpoint at 24 weeks. At 48 weeks, those initially assigned to Biktarvy will switch to islatravir plus ulonivirine. At 96 weeks, participants will start taking a new islatravir/ulonivirine single-tablet regimen.

At 24 weeks, 94.9% of people who switched to islatravir plus ulonivirine and 97.5% of those who remained on Biktarvy maintained viral suppression. No one on the new regimen and one person on Biktarvy (1.3%) had a viral load of 50 or higher. No participants had a viral load of 200 or higher, so on one met the criteria for drug resistance testing.

Treatment was safe and generally well tolerated. Drug-related adverse events were observed in ten people on islatravir plus ulonivirine and none of those who stayed on Biktarvy—a difference Luetkemeyer noted is not unusual in open-label switch studies. No one in either arm experienced severe or serious adverse events. One person on islatravir plus ulonivirine stopped study treatment due to a moderate skin reaction. Changes in CD4 and total lymphocyte counts were comparable in both groups.

Changes in CD4 and total lymphocyte counts were comparable in both groups, confirming that the low 2 mg islatravir dose is safe. Body weight changes were minor in both groups and not clinically meaningful. No one experienced hepatitis B reactivation.

These results support further development of this regimen, Luetkemeyer concluded. An islatravir/ulonivirine combination pill will be evaluated as a switch option in the forthcoming Phase III SYMPHORIA trials.

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