Once-Weekly Oral Treatment Keeps HIV Suppressed

Islatravir plus lenacapavir could be the first longer-acting regimen that doesn't involve injections.

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A once-weekly oral regimen of the approved HIV capsid inhibitor lenacapavir and the experimental antiretroviral islatravir can keep the virus suppressed as well as daily pills, according to study results presented this week at the Conference on Retroviruses and Opportunistic Infections (CROI 2024) in Denver.

Daily single-tablet regimens are highly effective, but some people have trouble taking pills every day. The long-acting injectable regimen Cabenuva (cabotegravir and rilpivirine) is the answer for some people, but others find it inconvenient to schedule injection appointments—or they simply don't like shots.

A Phase II clinical trial showed that more than 90% of people who switched to weekly islatravir and lenacapavir pills maintained an undetectable viral load, matching the viral suppression rate of those who stayed on daily Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine). If data continue to look promising, this could become the longest-acting regimen that doesn't involve injections.

"HIV treatment is not one size fits all—developing once-weekly treatment options could help meet the needs of each individual, aiming toward maximizing long-term outcomes for people with HIV," Jared Baeten, MD, PhD, vice president of HIV clinical development at Gilead Sciences, said in a press release. "These promising data presented at CROI help bring us one step closer to our goal of providing a wide range of options that may help transform the HIV treatment landscape."

Gilead's lenacapavir works differently than other antiretrovirals, so it remains active against HIV that has developed extensive resistance. A twice-yearly injectable version, sold as Sunlenca, was approved in 2022 for heavily treatment-experienced people with multidrug-resistant HIV. Gilead also makes a 300 milligram lenacapavir pill that is taken as an initial loading dose and can be used for temporary "bridging" if an injection must be missed.

Islatravir (also known as EFdAor MK-8591) is Merck's first-in-class nucleoside reverse transcriptase translocation inhibitor. It has a long half-life in the body, making it a candidate for long-acting HIV treatment and prevention. Combined with the NNRTI doravirine (Pifeltro) in a once-daily regimen,

it demonstrated good activity in previously untreated people and maintained viral suppression in those who switched from another oral regimen.

Islatravir has had a rocky road to get to this point. Because doravirine is not suitable for longer-acting treatment, Merck paired islatravir with its experimental NNRTI MK-8507 in a once-weekly regimen, and Merck and Gilead started a study of once-weekly islatravir plus lenacapavir in 2021. Later that year, however, the Food and Drug Administration (FDA) placed a clinical hold on islatravir after HIV-positive participants in treatment trials experienced a decline in CD4 T-cell counts and HIV-negative volunteers in pre-exposure prophylaxis (PrEP) studies saw a drop in total lymphocyte counts.

But Merck was not ready to give up on the drug. Company scientists conducted an extensive analysis to better understand the problem, determining that the islatravir doses used in these trials were too high. People who took a lower dose had CD4 and total lymphocyte numbers comparable to those of people on standard daily therapy or a placebo. The FDA lifted the hold, and Merck launched a new set of studies testing a lower daily dose of islatravir in combination with doravirine and resumed the trial with Gilead using a lower weekly dose of islatravir plus lenacapavir.

Now, the first results from that trial are finally here.

This open-label Phase II study (NCT05052996) enrolled 104 adults with viral suppression (less than 50 copies) on daily Biktarvy, no history of virological failure, a CD4 count of at least 350 and a total lymphocyte count of at least 900. People with hepatitis B were excluded as neither drug has activity against hepatitis B virus. The median age was 40 years, and 18% were women. The study population was diverse: 50% white, 36% Black, 29% Latino and 7% Asian, Native American or Pacific Islander.

The study participants were randomly assigned to either stay on Biktarvy once daily or switch to 2 mg islatravir and 300 mg lenacapavir pills once weekly. Islatravir plus lenacapavir was “both efficacious and well tolerated” at 24 weeks, and most participants in both groups maintained viral suppression, Amy Colson, MD, MPH, of Community Resource Initiative in Boston, told reporters at a media briefing.

Only one person (1.9%) in the islatravir plus lenacapavir group had a viral load above 50 at 24 weeks, and he went on to achieve viral suppression at 30 weeks. No one in the Biktarvy group had a detectable viral load at 24 weeks. The rate of viral suppression was exactly the same in the two groups (94.2%) after accounting for people with missing data. Follow-up will continue through 48 weeks.

Based on these findings, islatravir plus lenacapavir “has the potential to become the first oral weekly complete regimen” for the treatment of HIV, the researchers concluded.

Both treatment regimens were safe and generally well tolerated. Careful monitoring of CD4 cells and total lymphocytes revealed no clinically significant decreases and no differences between the two groups. Treatment-related adverse events were more common in the islatravir plus lenacapavir group (17% vs 6%), but all were mild to moderate. The most common side effects in the islatravir plus lenacapavir group were dry mouth and nausea. These data look good so far, but Colson noted that the study team wants to see 48-week safety data before any firm decisions are made about future studies.

“Our strategies for managing and treating HIV must evolve with the needs of the HIV community, and we are excited to have these promising first data from the Phase II study for islatravir and lenacapavir presented at CROI,” Elizabeth Rhee, MD, Merck’s vice president for global clinical development at Merck Research Laboratories, said in the press release. “Gilead and Merck remain committed to this collaboration and to the development of a potential once-weekly oral therapy for people living with HIV who may need additional options to help maintain viral suppression.”

Other researchers at the conference reported early data for weekly oral antiretrovirals further back in the pipeline, including another nucleoside reverse transcriptase translocation inhibitor (MK-8527), an integrase inhibitor (GS-1720) and a NNRTI (GS-5894).

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