Ulonivirine Shows Promise for Weekly Oral HIV Treatment

Study was halted early, but the novel NNRTI is now being tested with a lower dose of islatravir.

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Ulonivirine, an experimental non-nucleoside reverse transcriptase inhibitor, has the potential to become a component of once-weekly oral HIV treatment, according to Phase II study results presented at the International AIDS Society Conference on HIV Science (IAS 2025) in Rwanda.

Although the evaluated regimen of ulonivirine plus islatravir was discontinued due to declines in lymphocytes and CD4 T-cell counts—attributed to the high dose of islatravir—development of the combination is ongoing using a lower islatravir dose.

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

"A once-weekly oral regimen will likely improve lifelong adherence to treatment over a daily oral regimen," lead investigator Jean-Michel Molina, MD, of University of Paris Cité, suggested.

Ulonivirine (MK-8507), from Merck, is a novel potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against HIV strains that have developed resistance to older drugs in its class. Early studies showed that a single dose of ulonivirine monotherapy suppressed HIV in people new to treatment and its pharmacokinetics support once-weekly dosing.

HIV rapidly develops resistance to a single drug, so Merck tested ulonivirine in a weekly combination regimen with islatravir (MK-8591), the first nucleoside reverse transcriptase translocation inhibitor. But in late 2021, the Food and Drug Administration placed a clinical hold on trials of islatravir after some participants experienced declines in total lymphocyte and CD4 counts. Further investigation showed that the doses of islatravir used in these studies were too high, and some treatment trials later resumed using a lower dose.

At the IAS conference, Molina presented interim results from the study of ulonivirine plus islatravir, showing that the novel NNRTI still holds promise for long-acting oral treatment.

This Phase IIb trial enrolled 161 people who were currently on daily Biktarvy (bictegravir/tenofovir

alafenamide/emtricitabine) with viral suppression for at least six months. About 80% were men, two thirds were white, about a third were Black and the median age was 45 years. They had no history of treatment failure and did not have known NNRTI resistance mutations. More than 90% had a CD4 count over 350 at baseline (median 748).

The participants were randomly assigned to stay on the daily regimen or switch to islatravir (20 milligrams) plus one of three doses of ulonivirine (100, 200 or 400 mg) once weekly. The randomized part of the study was designed to run for 48 weeks with an open-label extension to 144 weeks. When the study was halted in November 2021, about eight months in, 153 people had reached the 24-week mark and 116 had available data.

Switching to ulonivirine/islatravir matched the efficacy of continuing on Biktarvy, and all participants maintained a viral load below 50. There were no cases of confirmed virologic failure in any group, Molina reported.

While overall adverse events rates were similar across the treatment groups, ulonivirine/islatravir recipients were more likely than Biktarvy recipients to experience drug-related adverse events (17.4% versus 10.0%) and to stop treatment for this reason (2.5% versus 0%). Side effects did not increase linearly with higher ulonivirine doses.

In particular, those on the experimental combination showed substantially larger decreases in total lymphocyte counts (mean -26.6% versus -2.5%) and CD4 counts (mean -23.9% versus -0.8%). Nonetheless, rates of infections—a possible consequence of white blood cell deficiencies—were similar across groups. These declines were reversible, and lymphocyte and CD4 counts returned toward baseline levels by 24 weeks after stopping the regimen.

Ulonivirine itself has not been implicated in lymphocyte and CD4 count declines. Unlike islatravir, ulonivirine does not inhibit DNA polymerase alpha and did not affect total lymphocyte or CD4 counts in laboratory studies or multiple animal models, according to Molina.

A new Phase IIb trial of once-weekly treatment using ulonivirine and a much lower 2 mg dose of islatravir is underway (NCT06891066). Merck and Gilead Sciences are also testing a weekly oral regimen of low-dose islatravir plus Gilead's HIV capsid inhibitor lenacapavir (Sunlenca), with promising results at 48 weeks.

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