Study of Weekly Oral HIV Treatment Resumes

The clinical trial will evaluate once-weekly islatravir plus Sunlenca pills for people switching from a daily antiretroviral regimen.

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Merck and Gilead Sciences have resumed a Phase II clinical trial of a once-weekly oral HIV treatment regimen that combines a lower dose of islatravir plus Sunlenca (lenacapavir), Merck announced on a recent earnings call.

Merck's islatravir (formerly known as MK-8591 or EFdA) is the first nucleoside reverse transcriptase translocation inhibitor. It has a long half-life in the body and has shown promise for long-acting HIV treatment and prevention.

Gilead's Sunlenca (formerly GS-6207), approved last December, is the first HIV capsid inhibitor. It is available as an oral tablet and an injectable formulation administered every six months. Studies showed that twice-yearly Sunlenca is highly effective, but it does not have an equally long-lasting partner, and it currently must be combined with daily oral meds. The longest-acting complete regimen, Cabenuva (cabotegravir plus rilpivirine), can be taken monthly or every other month, but it involves injections administered by a health care provider.

Islatravir appeared highly effective as a component of once-daily treatment in combination with Merck's NNRTI doravirine (Pifeltro), and pharmacokinetic studies showed that it lasts long enough in the body to be suitable for weekly dosing.

However, in December 2021, Merck announced that the Food and Drug Administration (FDA) had placed a clinical hold on trials of oral, injectable and implant formulations of islatravir due to unexpected safety concerns, and a study of islatravir plus lenacapavir was suspended.

This happened after trial data showed that HIV-positive people who received islatravir for treatment showed declines in their CD4 T-cell counts, while HIV-negative people in a study of islatravir for pre-exposure prophylaxis (PrEP) had decreased total lymphocyte counts.

But Merck was not ready to give up on islatravir and conducted extensive analyses to better understand the problem. Company scientists determined that the drug accumulates in lymphocytes, and high concentrations led to apoptosis, or cell death.

As Kathleen Squires, MD, of Merck, reported at this year's Conference on Retroviruses and Opportunistic Infections (CROI), the doses of islatravir used in earlier trials appear to have been too high, as larger decreases in CD4 and total lymphocyte counts were seen in people taking higher doses once weekly of treatment (20 milligrams) or once monthly for PrEP (60 milligrams).

A lower 0.75 dose of islatravir, taken once daily with doravirine, led to smaller CD4 cell declines compared with the higher doses: a mean of 19 and 38 cells in two switch trials reported at CROI. What's more, CD4 counts stabilized between 48 and 72 weeks. The risk of infections—a potential consequence of low T-cell levels—was not elevated among people taking islatravir, suggesting that this small decrease may have little clinical importance.

Further, researchers determined that participants in a dose-ranging study who took a 0.25 daily dose of islatravir had lymphocytes changes comparable to those seen in people taking a standard daily regimen of doravirine/tenofovir disoproxil fumarate/emtricitabine (Delstrigo).

Based on these findings, Merck has resumed clinical development of islatravir for HIV treatment. A 0.25 mg dose of islatravir is now being tested with doravirine as a once-daily regimen in new Phase III trials, and a 2 mg dose is being studied with oral Sunlenca as a once-weekly regimen. (Company-sponsored studies of once-monthly islatravir for PrEP have been discontinued, though independent researchers are evaluating long-lasting islatravir implants for HIV prevention.)

The islatravir plus Sunlenca treatment trial (NCT05052996) is currently recruiting people with HIV who have taken Gilead's Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine) for at least six months and have an undetectable viral load. They will be randomly assigned to either stay on Biktarvy or switch to low-dose islatravir and Sunlenca pills. After 48 weeks, those in the Biktarvy group will have the option to switch to oral islatravir plus Sunlenca.

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