Long-Acting HIV Therapy Hits a Snag

Studies of islatravir are put on hold after participants experience declining CD4 and lymphocyte counts.

December 22, 2021 By Liz Highleyman

UPDATE: On December 16, Michael Robertson, MD, of Merck Research Laboratories, gave an update on the status of islatravir to HIV community representatives. “We don’t have a full explanation right now,” he said. "The CD4 count is concerning, but the overall safety profile has been really excellent, so we don’t want to throw out the baby out with the bathwater."

Researchers do not yet understand what might be causing the decline in CD4 cells and other types of white blood cells. Merck did extensive animal studies prior to human trials and saw no signal of this adverse effect. While islatravir plus MK-8507 had an additive effect on CD4 counts, with the greatest decreases seen in those who received the highest doses of MK-8507, declines were also seen when islatravir was paired with doravirine or used alone.

Robertson explained that declines in CD4 counts were very small and subtle in trials of once-daily islatravir. In switch studies, people with well-controlled HIV who took daily islatravir plus doravirine experienced about a 40-cell decrease while those in the control group saw about a 30-cell increase. However, among people who received higher doses of islatravir once weekly, the effect was larger, with some study participants seeing a 50% drop and some falling below 200. In the PrEP program, total lymphocyte counts fell by about 20%, but levels remained within the normal range. CD4 T-cell levels, specifically, are usually not measured in healthy HIV-negative people. Lymphocyte changes appeared to be similar in men and women and people of different racial groups.

Researchers are continuing to follow study participants to see whether CD4 and total lymphocyte decreases are reversible and how long this takes. Once the mechanism becomes clearer, it may be possible to resume development of islatravir, perhaps with different dosing. While studies of MK-8507 are now on hold, Merck is also investigating whether that drug could go forward, possibly in combination with something other than islatravir.

UPDATE: On December 13, Merck announced that the Food and Drug Administration has placed a clinical hold on investigational new drug applications for the oral islatravir plus doravirine combination for HIV treatment, injectable islatravir for treatment and prevention, and oral and implant formulations of islatravir for PrEP. No new studies may be initiated. Participants in trials of islatravir plus doravirine trials will continue to receive the medication but no new participants will

be randomized (partial clinical hold). Those in studies of injectable islatravir or islatravir PrEP will no longer receive the drug, but investigators will continue to monitor their CD4 cell and total lymphocyte counts (full clinical hold). Altogether, six trials were put on a full hold and seven on a partial hold.

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Merck has put the brakes on two experimental long-acting antivirals, MK-8507 and islatravir, due to safety concerns in clinical trials, the company recently announced. Out of "an abundance of caution," Merck and Gilead Sciences also put a temporary hold on their study of islatravir plus lenacapavir for HIV treatment.

While daily antiretroviral therapy is highly effective, some people living with HIV are eager for treatment that can be taken less often. The long-acting injectable regimen Cabenuva (cabotegravir plus rilpivirine) is taken once monthly but requires clinic visits for administration. Long-acting oral pre-exposure prophylaxis (PrEP) is also a sought-after goal.

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 is being studied for both long-acting HIV treatment and prevention.

Islatravir has shown good activity in a once-daily combination with Merck's non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine (Pifeltro). At the recent European AIDS Conference, researchers reported that the regimen led to sustained viral suppression for 144 weeks in people new to treatment. In addition, data from the Phase III ILLUMINATE SWITCH trials showed than the combo maintained viral suppression for 48 weeks in people who switched from their current antiretroviral regimen.

While islatravir can be taken less frequently, doravirine is not suitable for long-acting therapy. So Merck paired islatravir with its experimental long-acting NNRTI MK-8507, which previously demonstrated promising safety and efficacy, in a once-weekly regimen evaluated in the Phase II IMAGINE-DR trial.

Islatravir is also being studied for PrEP, both as a once-monthly oral regimen and as an implant, which early studies suggest could provide protection against HIV for a year.

But a couple of weeks after the conference, Merck announced that it was halting the IMAGINE-DR study after people randomized to receive islatravir plus MK-8507 once weekly experienced a decline in their CD4 T-cell counts. The greatest decreases were seen in those receiving the highest doses of MK-8507. An independent data and safety monitoring committee recommended that dosing be stopped, although participants will continue to be monitored.

At the time, Merck said that while it had paused development of MK-8507, it "remains confident in

islatravir's overall profile." But a review of other studies called that confidence into question.

In its November 18 press release, Merck noted that small, treatment-related decreases in CD4 counts were observed in the ILLUMINATE SWITCH trials, in which islatravir was used with doravirine, not MK-8507. The decline in T cells was not linked to infections or other adverse events.

What's more, once-monthly islatravir used alone was associated with dose-dependent lymphocyte decreases among HIV-negative participants in a Phase II PrEP trial, although levels remained within the normal range.

On December 6, Merck announced that it is pausing enrollment in two Phase III trials, IMPOWER 22 and IMPOWER 24, evaluating monthly islatravir for PrEP, again on the recommendation of an external data monitoring committee. Participants who are already enrolled will continue to receive islatravir and will undergo additional monitoring, including more frequent CD4 cell and total lymphocyte measurements.

These concerns have also had an impact on Merck's collaboration with Gilead Sciences to study a long-acting combination of islatravir plus lenacapavir, Gilead's long-acting HIV capsid inhibitor, which has shown promise for both treatment and prevention.

On October 26, Gilead and Merck announced the start of a Phase II trial evaluating a once-weekly oral regimen of islatravir plus lenacapavir for people switching antiretroviral therapy. But a month later, enrollment was temporarily paused, according to the companies. Current participants will continue to receive the drugs with ongoing monitoring.

UPDATE: On December 21, Gilead announced that the FDA has also put a clinical hold on lenacapavir. However, unlike the islatravir holds, the lenacapavir action was prompted not by safety issues but rather by concerns about the suitability of the type of glass vials used for the injectable formulation. Dosing of oral formulations of lenacapavir will continue. The company "remains confident about the future potential of lenacapavir and is committed to resolving this vial quality issue."

While these developments are disappointing, Merck, Gilead and other companies are continuing to pursue long-acting antiretrovirals for HIV treatment and prevention.

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