Islatravir Shows Promise for Once-Monthly Oral PrEP

Monthly islatravir pills are just one of the long-acting options in the HIV prevention pipeline.

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Islatravir, the first of a new class of antiretrovirals, appeared to be well tolerated, reached levels adequate for HIV prevention and should work for at least a month, according to research presented this week at the virtual HIV Research for Prevention conference (HIVR4P).

If these findings are confirmed in larger studies, islatravir as a new option for long-acting pre-exposure prophylaxis (PrEP) could be "a huge potential game changer," International AIDS Society president Adeeba Kamarulzaman, MBBS, said at an HIVR4P press briefing in advance of the conference.

Merck's islatravir (formerly known as MK-8591 or EFdA), the first nucleoside reverse transcriptase translocation inhibitor, appears to have multiple mechanisms of action against HIV. Besides acting as a defective building block that halts construction of new viral DNA, it also works at a later step in the viral replication process.

Islatravir is being studied for both HIV prevention and treatment. Prior research showed that the drug is highly potent and has a long half-life in the body, suggesting it has the potential to be taken once weekly for treatment or once monthly—or even less often—for PrEP.

Researchers first reported in 2018 that low weekly oral doses of islatravir were highly protective against a hybrid simian-human virus (SHIV) in a series of animal studies. In a paper published last year, they reported that none of the monkeys that received the two higher tested doses of islatravir were infected with SHIV after multiple rectal exposures.

This research set the stage for human clinical trials. At HIVR4P, Sharon Hillier, PhD, of the University of Pittsburgh Magee-Womens Research Institute, presented early findings from an ongoing Phase IIa trial of once-monthly islatravir for PrEP.

This randomized, double-blind study is evaluating the safety, tolerability and pharmacokinetics of islatravir in adults at low risk for HIV. Participants were randomly allocated to receive six doses of 60 or 120 milligrams of islatravir or a placebo, all administered as tablets once monthly.

The study completed enrollment with 242 participants in November 2020. Hillier reported results from an interim analysis of 192 people who were randomized and started taking the tablets. About two thirds were women, 64% were white, 30% were Black and 16% were Latino; the median age was 32 years.

For the pharmacokinetic analysis, islatravir levels were measured in blood plasma, peripheral blood mononuclear cells (T cells and other immune cells) and biopsies of rectal, cervical and vaginal tissue.

People taking either the 60 mg or 120 mg tablets had trough levels of the active form of islatravir in their peripheral blood cells—meaning the lowest level between doses—that were well above the thresholds that provided full protection in monkeys and antiviral activity in people with HIV in a treatment study.

A preliminary analysis of tissue biopsies suggested that islatravir was rapidly distributed and reached adequate levels that were sustained between doses.

What's more, both doses of islatravir were well tolerated. Most adverse events were mild or moderate and resolved on their own. The most common adverse events were headache, diarrhea and nausea. There were no serious adverse events and no deaths, and only two people stopped treatment due to potentially drug-related adverse events.

Although these findings suggest that a lower dose or longer dosing interval would still work, Hillier explained that a conservative dosing regimen was chosen to allow for some degree of forgiveness—for example, if a person takes a pill late or even misses a dose. The 60 mg dose was selected for future clinical trials.

Last November, Merck and the Bill & Melinda Gates Foundation launched a Phase III trial called IMPOWER 22 that will evaluate the safety and efficacy of islatravir PrEP in cisgender women and adolescent girls at high risk for HIV in sub-Saharan Africa. Approximately 4,500 participants will be randomly assigned to receive once-monthly oral islatravir or once-daily Truvada (tenofovir disoproxil fumarate/emtricitabine).

Another planned trial, IMPOWER-024, will enroll cisgender men and transgender women who have sex with men in countries around the world. They will be randomized to receive once-monthly islatravir or once-daily Truvada or Descovy (tenofovir disoproxil fumarate/alafenamide), the latter of which is not yet approved for people exposed to HIV via vaginal sex.

An implantable formulation of islatravir is also being studied for PrEP. About the size of a matchstick, the implant releases a small amount of the drug over time, similar to implants used for long-acting contraception. An early study of HIV-negative volunteers showed that the implant delivered protective concentrations of the drug for more than a year.

On the treatment front, findings presented in October showed that a combination of once-daily

islatravir plus Pifeltro (doravirine) demonstrated good efficacy in a Phase IIb trial. After 96 weeks, 90% of people treated with the selected dose of islatravir plus Pifeltro had an undetectable viral load. But thanks to its long half-life, islatravir has the potential to be taken less often. Merck plans to evaluate islatravir plus its experimental non-nucleoside reverse transcriptase inhibitor MK-8507 as a once-weekly treatment regimen.

If the Phase III trials of oral islatravir PrEP go as planned, Hillier said she hoped it might be available by 2024.

Acknowledging that injectable cabotegravir PrEP administered every other month was recently shown to be more effective than daily Truvada both for men who have sex with men and for cisgender women, Hillier said she didn't think there would be "a single magic bullet" for HIV prevention. Some people may want to avoid injections, and others many find it more convenient to take a pill they can get from a pharmacy rather than seeing a health care provider every eight weeks for an injection.

Both a monthly pill and every-other-month injections would be good options for people who don't want to think about HIV prevention every day or who wish to be discrete about their PrEP use. "There's no pill bottle that rattles or that someone can find," Hillier said. "Once you swallow that pill or get that injection, no one will know."

"We're expanding the toolbox so people can pick the one that works for them," she added, regarding the variety of new options in the PrEP pipeline. "We're talking about choices among fantastic options that we didn't have just a couple years ago. We have such an abundance of riches."

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