

Doravirine/Islatravir HIV Treatment Combo Looks Good in Late-Stage Trials

Merck's experimental once-daily single-tablet regimen maintained an undetectable viral load in people who switched treatment.

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A once-daily combination pill containing doravirine and islatravir maintained viral suppression for 48 weeks in two Phase III trials, according to [top-line results announced by Merck](#). The company plans to present more detailed data at future scientific conferences and submit them to the Food and Drug Administration for approval.

Doravirine is Merck's next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI); it is sold alone as Pifeltro and as part of the Delstrigo coformulation (doravirine/tenofovir disoproxil fumarate/lamivudine). Islatravir (also known as EFdA or MK-8591) is a first-in-class nucleoside reverse transcriptase translocation inhibitor.

In prior studies, a once-daily regimen of doravirine plus islatravir [demonstrated good activity](#) in previously untreated people and [maintained viral suppression](#) in those who switched from another regimen. Islatravir's long half-life in the body makes it a candidate for longer-acting treatment and prevention, and it also [shows promise as part of a once-weekly regimen](#) with Gilead Sciences' capsid inhibitor lenacapavir (Sunlenca).

The development of islatravir [hit a snag](#) when HIV-positive participants in early treatment trials experienced a decline in CD4 T-cell counts and HIV-negative volunteers in prevention studies saw a drop in total lymphocyte counts, prompting the Food and Drug Administration (FDA) to place a clinical hold on the drug in late 2021. Merck scientists conducted an extensive analysis, determining that the doses used in these trials were too high. The FDA subsequently lifted the hold, and [HIV treatment studies resumed](#) using a lower dose; however, the development of islatravir for pre-exposure prophylaxis (PrEP) was halted.

Now, one-year results from two Phase III trials of treatment using a single-tablet regimen containing 100 mg of doravirine and 0.25 mg of islatravir show that the lower-dose combination looks effective without the same safety concerns.

Study MK-8591A-051 ([NCT05631093](#)) enrolled 551 adults with an undetectable viral load on various baseline antiretroviral regimens, while Study MK-8591A-052 ([NCT05630755](#)) included 513

people with viral suppression on Gilead's Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine) specifically. In both studies, participants were randomly assigned to switch to the doravirine/islatravir combination pill or stay on their current regimen. The first study was open-label, meaning investigators and participants knew which regimen they got, while the second was double-blind, meaning they did not know.

In both trials, doravirine/islatravir was non-inferior to the comparison regimens, meaning it worked equally well for maintaining viral suppression (below 50 copies) at 48 weeks. In the second trial, doravirine/islatravir did not meet the criteria for superiority over Biktarvy, but this is not unexpected, as Biktarvy's efficacy is hard to beat. Merck did not announce detailed viral suppression data, but efficacy typically exceeds 90% in such trials.

According to Merck, "primary safety objectives of both trials were also met." Again, details were not announced, but this suggests researchers did not see the type of blood cell declines that doomed the higher dose of islatravir. Reassuringly, careful monitoring of CD4 and total lymphocyte counts in the ongoing study of once-weekly lenacapavir plus islatravir revealed [no clinically significant decreases](#).

Having reach the 48-week milestone, all participants in Study MK-8591A-051 will receive doravirine/islatravir through 144 weeks, or about two and a half years. Those in Study MK-8591A-052 will remain on their randomized regimen through 144 weeks. At that point, eligible participants may continue on doravirine/islatravir through 240 weeks or until the combination pill becomes commercially available, whichever comes first.

"We are encouraged by the results from these Phase III trials evaluating a once-daily, oral, two-drug, single-tablet regimen of doravirine and islatravir," said Eliav Barr, MD, senior vice president and chief medical officer of Merck Research Laboratories, in a [news release](#). "We are committed to advancing our clinical programs for islatravir in combination with other antiretrovirals as potential options to help address the needs of people living with HIV."

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