

Doravirine/Islatravir Treatment Combo Shows Continued Promise

Merck's once-daily dual regimen was well tolerated and maintained viral suppression in most people who switched from standard treatment.

May 19, 2025 By [Liz Highleyman](#)

People who switched from standard oral antiretroviral therapy to a once-daily combination pill containing doravirine and islatravir maintained viral suppression for 48 weeks, according to a pair of late-stage studies presented at the [Conference on Retroviruses and Opportunistic Infections \(CROI 2025\)](#).

"Despite the availability of multiple daily antiretroviral therapies, the needs of people living with HIV are evolving," Chloe Orkin, MD, of Queen Mary University of London, said in a [Merck news release](#). "Many people living with HIV are older and also managing comorbidities, making it important to have daily treatment options that can help meet each person's unique health needs. I'm excited to see that doravirine/islatravir has potential as a new daily treatment option for people living with HIV who may benefit from this two-drug regimen."

Doravirine is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with a higher barrier to resistance than older drugs in its class; it is sold alone as Pifeltro and is 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 the combination pill [maintained viral suppression](#) in those who switched from another regimen. Islatravir has a long half-life in the body, making it a potential candidate for longer-acting treatment, and it has also [shown promise as part of a once-weekly regimen](#) with Gilead Sciences' capsid inhibitor lenacapavir (Sunlenca).

Islatravir's development [hit a snag](#) in 2021 when HIV-positive participants in earlier treatment trials experienced a decline in CD4 T-cell counts and HIV-negative volunteers in pre-exposure prophylaxis (PrEP) studies saw a drop in total lymphocyte counts. During a Food and Drug Administration (FDA) clinical hold, scientists conducted an extensive analysis and determined that the doses used in these trials were too high. The FDA subsequently lifted the hold, and [treatment studies resumed](#) using a lower dose.

In December, Merck [teased top-line data](#) from two Phase III trials testing a single-tablet regimen containing 100 milligrams of doravirine and the lower 0.25 mg dose of islatravir, showing that the combination pill appears effective without the same safety concerns. Orkin and Amy Colson, MD, MPH, of the Community Research Initiative in Boston, presented detailed results at CROI.

Orkin's study, MK-8591A-051 ([NCT05631093](#)), enrolled 551 adults with viral suppression on various two- or three-drug oral regimens. At study entry, they had a viral load below 50 for at least three months with no history of treatment failure or known resistance to doravirine. About 60% were men, 45% were Black, 39% were white, 15% were Latino and the median age was 51 years. The participants were randomly assigned to switch to doravirine/islatravir or stay on their current regimen. This study was open-label, meaning the investigators and participants knew who was taking which regimen.

Colson's study, MK-8591A-052 ([NCT05630755](#)), included 513 people with an undetectable viral load on Gilead's Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine). The entry criteria were the same. About 80% were men, 61% were white, 31% were Black, 23% were Latino and the median age was 47. Here, too, they were randomized to switch to doravirine/islatravir or stay on their current regimen. This study was double-blind, meaning investigators and participants did not know who was taking what.

In both trials, doravirine/islatravir was non-inferior to the comparison regimens, meaning it was equally likely to maintain viral suppression.

In the first trial, 95.6% of people who switched to doravirine/islatravir had an undetectable viral load at 48 weeks, compared with 91.9% of those who stayed on their current regimen. Conversely, 1.4% of people on doravirine/islatravir and 4.9% on a comparison regimen had a viral load above 50. Two of them showed virological failure at four weeks and stopped treatment early; both were found to have had multiple drug resistance mutations at baseline, meaning they should have been ineligible. The other three discontinued treatment after 48 weeks with a viral load above 200; no new resistance to doravirine or islatravir was detected. Based on these findings, doravirine/islatravir met the criteria for statistical superiority.

In the second study, 91.5% of doravirine/islatravir recipients had an undetectable viral load at 48 weeks, as did 94.2% of those who continued to take Biktarvy. Here, 1.5% of people who switched and 0.6% of those who stayed on Biktarvy had a viral load above 50. Two people on doravirine/islatravir had a confirmed viral load above 200, but no new resistance to doravirine or islatravir was detected. Here, doravirine/islatravir did not meet the bar for superiority, but this is not unexpected as Biktarvy's efficacy is hard to beat.

Doravirine/islatravir was safe and generally well tolerated. In Orkin's study, side effects were more than twice as common with doravirine/islatravir (12% versus 5%), but in that group, there were no drug-related serious adverse events or discontinuations for this reason. In Colson's study, the frequency of side effects was similar in both groups (about 10%), but there was one drug-related serious adverse events leading to discontinuation (immune thrombocytopenia).

Participants did not experience the type of white blood cell declines that doomed higher doses of islatravir. Changes in CD4 and total lymphocytes were similar in people who switched and those who stayed on their current regimen. In both studies, kidney function biomarkers remained stable in the doravirine/islatravir group but declined in the comparison groups. Kidney toxicity is a known side effect of tenofovir disoproxil fumarate but less so with the newer tenofovir alafenamide in Biktarvy.

Weight gain is a growing concern for people with HIV, but its association with various antiretroviral regimens remains unclear. In Colson's study, weight remained roughly stable in both treatment groups. In Orkin's study, some participants taking doravirine/islatravir did gain weight, but this was driven by those who switched away from tenofovir disoproxil fumarate or efavirenz (Sustiva), which are known to have a suppressive effect on weight.

Importantly, Biktarvy and most other standard oral regimens contain one of the two versions of tenofovir and either emtricitabine or lamivudine, which are also active against hepatitis B virus (HBV). Doravirine and islatravir are not, so people with active HBV infection were excluded from the trials. Nonetheless, three people with possible latent infection experienced low-level HBV viral load without liver enzyme elevations, and two people were newly diagnosed with acute HBV. Doravirine/islatravir may not be an appropriate option for people with HIV/HBV coinfection, and those who are HBV negative should be vaccinated, Colson said.

Having reached 48 weeks, all participants in Orkin's study will be offered doravirine/islatravir with continued monitoring through 144 weeks. Those in Colson's study will stay on their randomized assigned regimen through 144 weeks. Merck indicated that it plans to begin submitting applications for regulatory review by the middle of this year.

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