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Doravirine/Islatravir Combo Pill Could Soon Be a New HIV Treatment Option

The once-daily oral regimen works well for initial treatment and as a switch option for people with viral suppression.

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An experimental once-daily combination pill containing doravirine and islatravir (DOR/ISL) works as well as the widely used Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine) pill for people starting HIV treatment for the first time, according to study results presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2026) last week in Denver.

What's more, updated results from two other late-stage clinical trials show that DOR/ISL continues to maintain viral suppression when people switch from a standard daily oral antiretroviral regimen. Merck has already submitted data from these studies to the Food and Drug Administration, and an approval decision is expected in late April.

Doravirine (sold alone as Pifeltro and part of the Delstrigo coformulation) is a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with a high barrier to resistance. Islatravir is a first-in-class nucleoside reverse transcriptase translocation inhibitor. Development of islatravir hit a snag in 2021 when some participants in earlier trials saw a decrease in their CD4 T-cell or total lymphocyte counts. But scientists determined that the doses used in those studies were too high, and this side effect has not been seen using the lower dose in the new combination pill.

Merck is evaluating the once-daily single-tablet regimen, which contains 100 milligrams of doravirine and 0.25 mg islatravir, both as a switch option for people with viral suppression and as first-line treatment.

Switching Treatment

As reported at last year's CROI, DOR/ISL maintained viral suppression at 48 weeks in pair of Phase III trials, one that enrolled people on Gilead Sciences' Biktarvy at baseline (MK-8591A-052; NCT05630755) and another that enrolled people on various two- or three-drug oral regimens (MK-8591A-051; NCT05631093). In both studies, participants were randomly assigned to switch to DOR/ISL or stay on their current regimen.

Updated results presented at this year's conference showed that the combination pill continued to

control HIV at two years. In the first study, 88.9% of people randomized to DOR/ISL maintained an undetectable viral load (below 50) at 96 weeks, compared with 90.1% of those who stayed on Biktarvy. In the second trial, 92.6% of people who were initially assigned to DOR/ISL and stayed on it for the whole study maintained viral suppression through 96 weeks, as did 96.6% of those who switched to DOR/ISL at 48 weeks.

Further data from these trials, presented at last year's European AIDS Conference (EACS 2025), showed that DOR/ISL was associated with minimal changes in weight or body composition and had no clinically meaningful effect on lipid or blood sugar levels or insulin resistance.

"As people living with HIV age, managing other health conditions becomes a reality for many, making it especially important to have treatment options that can help meet each person's unique health needs," MK-8591A-052 investigator Amy Colson, MD, of the Community Resource Initiative in Boston, said in a Merck news release. "Over time, people may need to adjust their HIV treatment regimens because of comorbidities, concerns about toxicities, tolerability challenges or a desire for regimens with fewer medications. These 96-week data are encouraging, showing a non-INSTI option like investigational DOR/ISL could offer an important alternative."

First-Line Treatment

Turning to first-line treatment, Merck announced top-line results from the Phase III MK-8591A-053 trial (NCT05705349), comparing DOR/ISL versus Biktarvy as an initial regimen, late last year. Jürgen K Rockstroh, MD, of University Hospital Bonn in Germany, presented details at CROI; the results were simultaneously published in The Lancet HIV.

This study enrolled 536 previously untreated adults from 20 countries in North and South America, Europe, Africa and Asia. The median age was 32 years, 75% were men and the population was racially and ethnically diverse. About half had HIV-1 subtype B (the most common type in the Americas and Europe), 19% had subtype C (most common in Africa) and 28% had other subtypes.

At baseline, they had a median viral load of 55,000, and 10% had a very high virus level above 500,000. The median CD4 count was 370, but 17% had a count below 200, indicating an AIDS diagnosis. Rockstroh noted that, even today, a large proportion of people are diagnosed with HIV and start treatment late, after they have already experienced substantial immune impairment.

The participants were randomly assigned to start treatment with DOR/ISL or Biktarvy, both taken once daily. Rockstroh presented primary outcome results at 48 weeks; follow-up will continue through 144 weeks.

At 48 weeks, 91.8% of people taking DOR/ISL and 90.6% of those taking Biktarvy had an undetectable viral load. Six people (2.2%) on DOR/ISL and nine people (3.4%) on Biktarvy had a viral load of 50 or higher. These results show that DOR/ISL is noninferior to Biktarvy for initial treatment. Efficacy was similar regardless of baseline viral load, CD4 count or HIV subtype. However, two people—both with very high virus levels and low CD4 counts—showed evidence of

treatment-emergent resistance to doravirine and islatravir.

DOR/ISL was safe and generally well tolerated, Rockstroh reported. CD4 cell gains were similar in the DOR/ISL and Biktarvy groups (218 and 226, respectively), and participants did not experience the kind of CD4 or lymphocyte declines that doomed higher doses of islatravir.

The frequency of drug-related adverse events (14.1% versus 18.0%) and severe drug-related events (1.1% versus 1.5%) were comparable in the DOR/ISL and Biktarvy groups. Two people in the DOR/ISL group and one person in the Biktarvy group discontinued treatment for this reason. Increases in body weight were similar in the two groups (about 8 pounds). Rockstroh noted that some weight gain is expected when people first start HIV treatment.

Importantly, neither doravirine nor islatravir are active against hepatitis B virus (HBV), unlike tenofovir alafenamide in Biktarvy. There were three reported HBV infections in the DOR/ISL group, all of whom tested negative for active hepatitis B—as required—at study entry. This underscores the importance of hepatitis B vaccination for people who are not already immune. Rockstroh said study participants were encouraged to get vaccinated, but not everyone complied.

“These new Phase III results are meaningful, showing that an investigational two-drug regimen without an [integrase inhibitor] demonstrated noninferior efficacy and a comparable safety profile versus [Biktarvy] in previously untreated adults with HIV-1, including those with advanced disease,” Rockstroh said in the news release. “These findings add to the growing evidence supporting the potential role of DOR/ISL in HIV care.”

Islatravir has a long half-life in the body, making it a potential candidate for longer-acting treatment. It has shown good results as part of a once-weekly oral regimen in combination with Gilead Sciences’ capsid inhibitor lenacapavir (Sunlenca); two-year Phase II data were presented at EACS 2025. An islatravir/lenacapavir combination pill is now being tested as a switch option in the Phase III ISLEND-1 (NCT06630286) and ISLEND-2 (NCT06630299) trials, with initial results expected this Spring.

Merck is also testing a once-weekly regimen of islatravir and its investigational NNRTI ulonivirine in a Phase II trial (MK-8591B-060; NCT06891066). Data from a laboratory study presented at CROI showed that islatravir plus ulonivirine suppressed viral breakthrough more effectively and demonstrated a higher barrier to resistance than either drug alone.

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