Bictegravir Plus Lenacapavir Could Simplify Treatment for People on Complex Regimens

The two-drug oral combination worked as well as regimens containing multiple pills, setting the stage for a new single-tablet regimen.

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A once-daily oral combination of bictegravir and lenacapavir could enable simpler HIV treatment for people taking complex antiretroviral regimens, according to study results presented at the International AIDS Conference (#AIDS2024) in Munich. Gilead Sciences is now testing a new single-tablet regimen containing the two drugs.

Standard antiretroviral therapy is highly effective for most people living with HIV, but some individuals with long-term infection have developed drug resistance that renders certain medications ineffective, while others may be unable to tolerate nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). These people may need to use complex drug combinations and thus cannot benefit from the convenience of a single-tablet regimen. Around 8% of people with HIV use regimens containing two or more daily pills.

Bictegravir is a once-daily oral integrase inhibitor best known as a component of the widely used Biktarvy combination pill (bictegravir/tenofovir alafenamide/emtricitabine). Lenacapavir is the first HIV capsid inhibitor, which disrupts the cone-shaped shell surrounding the viral genetic material and enzymes. It is typically administered by injection every six months, but it does not yet have any other partner drugs that can be taken at such a long interval. Lenacapavir is now approved only as a switch option in combination with daily meds for people with multidrug-resistant HIV. It also comes in an oral formulation that is used as an initial loading dose before starting injections. A single-tablet regimen containing these two drugs is in development.

Sorana Segal-Maurer, MD, of New York-Presbyterian Queens, and colleagues conducted the ARTISTRY-1 trial (NCT05502341) to evaluate the safety and efficacy of bictegravir plus lenacapavir as a consolidation option for people who have achieved viral suppression on complex regimens. These were defined as two or more pills per day, more than once-daily dosing, a boosted protease inhibitor or NNRTI with one or more additional drugs besides NRTIs, or injectable drugs other than Cabenuva (long-acting cabotegravir and rilpivirine).

This multicenter open-label Phase II/III study enrolled 128 people with HIV. Nearly 20% were women, 65% were white, 31% were Black and 16% were Latino. The median age was 60 years, they had been on treatment for a median of 27 years and they had tried a median of six prior antiretrovirals. The median CD4 T-cell count was 610, but 20% had a past history of AIDS. They were required to have adequate kidney function and could not have hepatitis B virus (HBV) coinfection, as neither bictegravir nor lenacapavir are active against HBV.

At baseline, the study participants were on stable complex regimens for at least six months. The most common reason for using such regimens was drug resistance (81%). They were taking a wide variety of combinations that included up to nine (median three) pills per day. Many were on a protease inhibitor plus an integrase inhibitor. More than 40% were taking two pills per day, 19% were taking three, 11% were taking four and 27% were taking five or more. About 40% had to take meds twice daily.

The participants were randomly assigned in a 2:2:1 ratio to receive a once-daily regimen of 75 milligrams oral bictegravir plus 25 mg oral lenacapavir or 75 mg bictegravir plus 50 mg lenacapavir, taken as separate pills, or to stay on their current regimen.

At this year's Conference on Retroviruses and Opportunistic Infections (CROI), researchers presented data showing that at six months, most people who switched to one of the bictegravir plus lenacapavir regimens maintained viral suppression. The combinations continue to be effective and well tolerated at one year, Segal-Maurer reported at AIDS 2024.

Among the participants assessed at 48 weeks, 47 of the 51 people (92%) in the 75 mg bictegravir plus 25 mg lenacapavir group and 47 of the 52 people (90%) in the 75 mg bictegravir plus 50 mg lenacapavir group had a viral load below 50, as did everyone who stayed on their baseline regimen. Two people taking the lower lenacapavir dose had HIV RNA above this threshold but regained viral suppression without changing treatment. One person in the higher-dose group also had a viral load above 50 and regained suppression after switching to a new regimen. Changes in CD4 counts were comparable across the three groups.

Bictegravir plus lenacapavir was generally safe and well tolerated. The most common adverse events after starting treatment were COVID-19, upper respiratory tract infections, diarrhea, joint pain and cough. For unclear reasons, treatment-related adverse events were three times more common in the lower-dose lenacapavir group, though the numbers were small. About 2% of people in both bictegravir plus lenacapavir groups discontinued therapy due to treatment-emergent adverse events.

"Bictegravir plus lenacapavir was highly effective in maintaining viral suppression over 48 weeks in participants switching from a complex regimen," the researchers concluded. "These findings support continued evaluation of the combination of bictegravir and lenacapavir to optimize treatment in virally suppressed people with HIV who are receiving complex regimens."

Given these promising results, the Phase III portion of this study will evaluate a bictegravir/lenacapavir single-tablet regimen using the 50 mg lenacapavir dose. In addition, the

Phase III ARTISTRY-2 trial (NCT06333808) is comparing the bictegravir/lenacapavir single-tablet regimen versus Biktarvy.

Longer-Acting Options

Meanwhile, Gilead continues to explore several longer-acting treatment candidates.

In another study presented at CROI, researchers reported that a once-weekly oral regimen of lenacapavir plus Merck's nucleoside reverse transcriptase translocation inhibitor islatravir kept HIV suppressed as well as daily pills. Though not yet being formally tested in clinical trials, real-world evidence suggests that a long-acting injectable regimen of lenacapavir plus cabotegravir could be a feasible option for people with NNRTI resistance.

Another trial at CROI, with follow-up data resistance data presented at AIDS 2024, suggested that lenacapavir plus two broadly neutralizing antibodies, teropavimab (GS-5423) and zinlirvimab (GS-2872), might be a durable combination, though this study has been hampered by COVID-19 disruptions and a temporary clinical hold on lenacapavir in 2022; additional evaluation is underway.

Further back in the pipeline, a preclinical pharmacology study and the first human study in HIV-negative volunteers showed that a new oral prodrug of lenacapavir, dubbed GS-4182, was well tolerated and appears suitable for once-weekly dosing. GS-1720, a long-acting oral integrase inhibitor, is also a candidate for weekly treatment. Preclinical data presented at AIDS 2024 showed that the drug has greater antiviral potency than bictegravir, while the first human trial showed that it is generally well tolerated and has a half-life that supports once-weekly dosing. If these drugs continue to show promise, GS-4182 and GS-1720 could potentially be combined in the first weekly capsid inhibitor/integrase inhibitor single-tablet regimen.

Click here to read the bictegravir plus lenacapavir study abstract.

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