Twice-Yearly Lenacapavir Could Be an Option for Initial HIV Treatment

The long-acting injectable antiretroviral helps maintain long-term viral suppression, but it still needs equally durable partners.

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Lenacapavir, a long-acting injectable administered once every six months, could be a component of combination regimens for people starting HIV treatment for the first time, according to final results from the CALIBRATE study. After 132 weeks of treatment, nearly 100% of participants maintained viral suppression.

A first-line HIV regimen administered just twice a year would be a welcome development. Long-acting treatment is more convenient, more discreet and encourages better adherence. But with no other equally durable meds currently available, lenacapavir must be used with daily antiretrovirals for HIV treatment.

In 2022, the Food and Drug Administration (FDA) approved Gilead Sciences' lenacapavir (brand name Sunlenca) as a component of combination therapy for heavily treatment-experienced people with multidrug-resistant HIV. The first approved HIV capsid inhibitor, lenacapavir works differently than older antiretrovirals, so it remains active against virus that has developed resistance to other drugs.

Since then, lenacapavir has become better known as a long-acting pre-exposure prophylaxis (PrEP) option. Studies showed that twice-yearly lenacapavir administered alone provides nearly complete protection against HIV acquisition. The FDA approved lenacapavir for PrEP (brand name Yeztugo) in June. While a single antiretroviral is enough to prevent HIV, treatment requires a combination approach that targets two or more steps of the viral life cycle.

Now, updated study results confirm that injectable lenacapavir also shows promise as a component of first-line combination HIV treatment.

The Phase II CALIBRATE trial (NCT04143594) enrolled 183 previously untreated people with HIV between November 2019 and August 2020. The study population was racially diverse—about half Black and 45% Latino—but more than 90% were men. About one in six started with a high viral load above 100,000 copies, and the median CD4 T-cell count was approximately 450.

Study participants were randomly allocated to four groups. Groups 1 and 2 received twice-yearly lenacapavir injections plus daily tenofovir alafenamide (TAF) and emtricitabine (the drugs in Descovy) for 28 weeks, then dropped back to a single oral drug, either TAF or bictegravir. Group 3 received daily lenacapavir pills plus TAF/emtricitabine. Group 4 received daily oral bictegravir, TAF and emtricitabine (the drugs in Biktarvy).

Researchers reported 28-week results at the 2021 International AIDS Society Conference on HIV Science, showing that 94% of people in Group 1 and 92% in Group 2 had an undetectable viral load (below 50 copies), as did 94% of those in Group 3 and 100% of those in Group 4. Two years later, investigators reported 54-week data in The Lancet HIV, showing that 90% of participants in Group 1, 85% in Group 2, 85% in Group 3 and 92% in Group 4 had undetectable virus.

Debbie Hagins, MD, of Coastal District CARE Clinic in Savannah, Georgia, and colleagues recently published final data from the study in the journal AIDS. At 80 weeks, 87% of people in Group 1, 75% in Group 2, 87% in Group 3 and 92% in Group 4 maintained viral suppression. Participants in all four groups gained around 250 CD4 cells. Group 4 concluded the trial at that point. At 132 weeks, after excluding missing data, viral suppression rates for Groups 1, 2 and 3 ranged from 98% to 100%. Four people developed lenacapavir resistance mutations.

Treatment was safe and generally well tolerated. No serious treatment-related adverse events were reported, but two people in Group 1 and three in Group 2 discontinued lenacapavir due to adverse reactions. The most common side effect in Groups 1 and 2 was injection-site reactions such as redness, swelling or pain, mostly mild to moderate.

“Lenacapavir-containing combinations achieved and maintained high rates of virologic suppression in treatment-naive participants through Week 132,” the study authors concluded. “These data support future development of lenacapavir-containing regimens for HIV-1 treatment.”

While a twice-yearly first-line regimen would be a game-changer, injectable lenacapavir is not there yet, as it must be taken with daily pills. The only complete long-acting regimen, Cabenuva (injectable cabotegravir and rilpivirine), is administered every other month, but it is currently approved only for people who are switching from daily treatment with an undetectable viral load.

Researchers are now exploring other therapies that could be given at longer intervals. Gilead is testing two long-acting injectable integrase inhibitor candidates (GS-1219 and GS-3242) and a pro-drug of islatravir (GS-1614). ViiV Healthcare is working on long-acting injectable formulations of a third-generation integrase inhibitor (VH-184) and an experimental capsid inhibitor (VH-499) after seeing good results with oral versions. Combining injectable lenacapavir and cabotegravir may also be a feasible approach, according to a case series of treatment-experienced people who had trouble adhering to daily pills.

Looking beyond antiretrovirals, scientists are also exploring broadly neutralizing antibodies (bnAbs) for long-acting HIV treatment.

Gilead is testing a pair of bnAbs, teropavimab (GS-5423) and zinlirvimab (GS-2872), as potential

partners for lenacapavir. At this year's Conference on Retroviruses and Opportunistic Infections, researchers reported results from a Phase II trial (NCT05729568) of lenacapavir, teropavimab and zinlirvimab—dubbed LTZ—for people with viral suppression on daily oral treatment. At 26 weeks, 96% of participants who switched to the LTZ regimen administered every six months maintained an undetectable viral load; the study is ongoing.

ViiV, likewise, is working on a bnAb known as N6LS as a partner for long-acting cabotegravir. In a Phase IIb study (NCT05996471), 96% of people with viral suppression who switched from a standard regimen to monthly cabotegravir injections plus N6LS administered by IV infusion every four months maintained viral suppression. The second part of the study will evaluate cabotegravir given every two months plus N6LS every six months.

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