Lenacapavir Plus Broadly Neutralizing Antibodies Maintains Viral Suppression

If approved, this combination could be the first complete twice-yearly HIV treatment regimen.

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Nearly 90% of people treated with lenacapavir plus two broadly neutralizing antibodies (bnAbs) from Gilead Sciences maintained viral suppression for a year, according to study findings presented at the European AIDS Conference in Paris (EACS 2025). If these results are confirmed in larger studies, this could potentially become the longest-acting HIV treatment regimen.

Onyema Ogbuagu, MBBCh, of Yale University, and colleagues conducted a Phase II clinical trial (NCT05729568) of lenacapavir, teropavimab and zinlirvimab (LTZ) for people currently on antiretroviral therapy with viral suppression.

People living with HIV normally produce HIV-specific antibodies, but these mostly target parts of the virus that are hidden or highly variable. However, a small proportion naturally make broadly neutralizing antibodies that target conserved parts of the virus. Teropavimab (GS-5423) is derived from a bnAb called 3BNC117 that targets HIV's CD4 binding site. Zinlirvimab (GS-2872) is derived from 10-1074, a bnAb that binds to the V3 loop on HIV's surface. Specialized antibodies are being explored for HIV prevention, treatment and a functional cure, but the virus can develop resistance to them, so they are best used in combination therapy.

Lenacapavir, the first HIV capsid inhibitor, is administered by injection every six months. It was approved in 2022 for highly treatment-experienced people with multidrug-resistant HIV and this past June for pre-exposure prophylaxis. While lenacapavir alone is highly effective for HIV prevention, it needs to be combined with other meds for treatment. There are currently no equally long-acting antiretrovirals, but bnAbs could potentially fill this gap.

The Phase II study enrolled 80 participants whose HIV was highly sensitive to both teropavimab and zinlirvimab according to phenotypic resistance testing. Most (85%) were men, about 55% were white, 36% were Black and a quarter were Latino. The median age was 51, and they had been on antiretrovirals for a median of about 14 years. At study entry, they had an undetectable viral load (below 50 copies) on a standard daily oral antiretroviral regimen for at least a year, and they had well preserved immune function, with a median CD4 count above 700.

After antibody sensitivity screening, 53 people were randomly assigned to switch to lenacapavir

plus the two bnAbs while 27 stayed on daily pills. The group that switched received subcutaneous injections of lenacapavir every six months (after an oral loading dose) and IV infusions of teropavimab and zinlirvimab (both 2,550 milligrams) on the same schedule.

At this year's Conference on Retroviruses and Opportunistic Infections, Ogbuagu presented primary results showing that 96% of people in both treatment groups maintained viral suppression at 26 weeks. At EACS, he presented follow-up results showing that the combination was still working well at 52 weeks: 89% of people who switched to LTZ and 93% of those who stayed on their daily oral regimen had a viral load below 50. CD4 counts increased, with no significant difference between the two groups (median +32 and +38 cells, respectively).

Three people taking lenacapavir plus the two bnAbs had confirmed viral rebound. One person had a viral blip at 12 weeks and higher rebound at 24 weeks. They developed resistance to lenacapavir and lost sensitivity to zinlirvimab. They restarted Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine) and regained viral suppression. The second and third participants both saw their viral load start to rise around 38 weeks, and the researchers put the time of viral rebound at 50 weeks. The second participant also lost sensitivity to zinlirvimab and regained viral suppression after restarting daily oral meds. The third participant did not develop resistance to lenacapavir, teropavimab or zinlirvimab; they had persistent low-level viremia for about 20 weeks after restarting Biktarvy.

At IDWeek, Gilead researchers presented further details about LTZ pharmacokinetics and anti-drug antibodies (ADAs), or treatment-emergent antibodies that target the bnAbs. Lenacapavir, teropavimab and zinlirvimab remained well above therapeutic levels over time. The half-lives of teropavimab and zinlirvimab were 63.5 and 89.1 days, respectively. Six people (11%) developed low levels of ADAs against teropavimab and nine (17%) developed antibodies against zinlirvimab—including five with ADAs against both bnAbs—but these were not associated with pharmacokinetics, viral rebound or adverse events.

The LTZ regimen was safe and generally well tolerated, with no severe side effects. The frequency of adverse events overall was about the same in both groups. No one who switched to LTZ stopped treatment due to adverse events; one person who stayed on their oral regimen stopped due to metastatic pancreatic cancer. The most common side effect in the LTZ group was mild to moderate lenacapavir injection site reactions, reported by 68%. About 40% of LTZ recipients developed nodules, which can occur where lenacapavir forms a depot under the skin. There were no infusion-related reactions to teropavimab or zinlirvimab.

Looking at patient-reported outcomes, 42 of the 53 participants who switched to the LTZ regimen completed HIV treatment preference questionnaires at study entry, 26 weeks and 52 weeks. Of these, 76% said they preferred lenacapavir plus the two bnAbs over daily pills, and 90% said the twice-yearly injectable regimen would be easier to adhere to.

"These data support further evaluation of lenacapavir, teropavimab and zinlirvimab in Phase III studies," the researchers concluded. "This long-acting combination regimen has potential as the

first complete twice-yearly combination treatment for people with HIV-1."

In the extension phase of this Phase II study, people randomized to LTZ will continue on the combination, while those who were assigned to stay on their baseline oral regimen will have an opportunity to switch to LTZ after 52 weeks. Gilead indicated that plans for Phase III are underway.

The Food and Drug administration has granted the LTZ regimen a Breakthrough Therapy Designation, intended to speed development of new therapies that may demonstrate substantial improvement over available treatment. A drawback of the regimen is that potential recipients need to be screened in advance for sensitivity to the bnAbs. In pre-screening for this trial, about half had HIV that was not susceptible to teropavimab, zinlirvimab or both.

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