

Lenacapavir Plus Broadly Neutralizing Antibodies Could Be Twice-Yearly Treatment

Most people who used the long-acting antiretroviral plus two experimental HIV antibodies maintained viral suppression for six months.

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Two broadly neutralizing antibodies, teropavimab and zinlirvimab, might be good partners for lenacapavir in a long-acting HIV treatment regimen, according to a study presented at the [2024 HIV Drug Therapy](#) meeting in Glasgow. The findings underscore the importance of screening for virus sensitivity to the antibodies but suggest that even people with partial resistance can still benefit if doses are high enough.

[Lenacapavir \(Sunlenca\)](#), which is administered by injection every six months, is approved for heavily treatment-experienced people with multidrug-resistant HIV. However, it currently does not have equally durable partners to build a complete twice-yearly regimen, so for now it must be used with daily oral antiretrovirals.

Broadly neutralizing antibodies (bnAbs) have the potential to fill that role. People with HIV normally produce antibodies against the virus, but these usually target parts that are highly variable, so they do not recognize new viral mutations. However, a small proportion of individuals naturally produce bnAbs that target conserved parts of the virus that don't change much. Research has shown that bnAbs show promise for HIV [prevention](#), [treatment](#) (especially [for children](#)) and [functional cure](#), but their utility has been limited by viral resistance.

Paul Cook, MD, of East Carolina University, and colleagues evaluated a triple combination regimen of lenacapavir plus a pair of bnAbs, teropavimab and zinlirvimab, all from Gilead Sciences.

Lenacapavir is the first approved HIV capsid inhibitor. Teropavimab (GS-5423) is derived from a bnAb called 3BNC117 that targets the CD4 binding site on HIV's gp120 protein, which the virus uses to enter cells. Zinlirvimab (GS-2872) is derived from a bnAb dubbed 10-1074 that binds to the V3 loop of HIV's envelope. Both bnAbs were modified to extend their half-life and enable less frequent dosing. Prior research found that around half of subtype B HIV—the most common type in the United States and Europe—is highly susceptible to both antibodies, and around 90% is sensitive to at least one.

The Phase Ib trial ([NCT04811040](#)) enrolled 32 people on standard oral antiretroviral treatment with an undetectable viral load (below 50 copies) for at least 18 months and a CD4 T-cell count of at least 500. They were screened at baseline to ensure that their HIV was highly sensitive to both teropavimab and zinlirvimab (primary cohort) or only one of the antibodies (pilot cohort).

At the start of the study, after discontinued their oral antiretrovirals, the participants received an oral loading dose of lenacapavir, subcutaneous injections of lenacapavir and an intravenous infusion of teropavimab (30 milligrams per kilogram). In addition, they were randomly assigned to receive either 10 mg/kg or 30 mg/kg infusions of zinlirvimab. The trial was supposed to run for a year, but due to a [temporary clinical hold on lenacapavir](#), participants received only one semiannual round of treatment.

Of the 21 participants in the primary cohort, 10 people in each dose group received the full treatment regimen. More than 80% were men and a majority were white. As reported at the [2023 Conference on Retroviruses and Opportunistic Infections](#) and in [The Lancet HIV](#), 90% of people in both dose zinlirvimab groups maintained an undetectable viral load at 26 weeks. One person in the lower-dose group experienced viral rebound and one participant in the higher-dose group withdrew from the study.

These findings set the stage for the pilot cohort of 11 people with virus that was highly sensitive to either teropavimab or zinlirvimab but not both. This cohort was more diverse: About a quarter were women, more than a third were Black and 27% were Latino. One person was diagnosed with hepatitis B and excluded from the analysis. At 26 weeks, eight of the remaining 10 (80%) maintained viral suppression, but response differed according to the zinlirvimab dose. Two of the four people who received the lower dose still had an undetectable viral load, compared with all six of those who received the higher dose.

At the Glasgow meeting, Cook presented results from a combined analysis of all 32 study participants; 21 were susceptible to both bnAbs, 5 were sensitive to teropavimab only and 6 were susceptible to zinlirvimab only. Sixteen were randomly assigned to each zinlirvimab dose group. Three did not complete the treatment regimen.

At 26 weeks, 26 of the 32 (81%) maintained viral suppression. Three people assigned to the lower dose of zinlirvimab had a detectable viral load (20 copies or higher), but none of the 15 people on the higher dose experienced viral rebound.

In the lower-dose group, one person had a detectable viral load (543 copies) despite being sensitive to both bnAbs; this individual regained viral suppression after resuming oral treatment but developed a lenacapavir resistance mutation. Another person, who was not sensitive to teropavimab, also restarted oral treatment and regained viral suppression. The third, who was not sensitive to zinlirvimab, had a low but detectable viral load that rose after a bout of COVID-19 and remained detectable even after restarting oral treatment.

The combination regimen was safe and generally well tolerated, with no drug-related serious

adverse events or withdrawals due to side effects. The most common side effect was lenacapavir injection site reactions, such as pain, swelling or nodules, most of which were mild to moderate. There were no differences in safety or tolerability between the two znlirvimab dose groups.

“These early-phase results suggest that high treatment efficacy for the long-acting regimen of lenacapavir, teropavimab and high-dose znlirvimab can be achieved when at least one antibody is highly active in people with HIV highly susceptible to one or both bnAbs,” the researchers concluded.

Based on these findings, a larger and longer Phase II trial of the triple combination using the higher znlirvimab dose is now underway ([NCT05729568](#)).

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