



Broadly Neutralizing Antibodies Show Promise for Long-Acting HIV Treatment

Specialized antibodies might be partners for injectable lenacapavir or cabotegravir in twice-yearly regimens.

March 24, 2025 By [Liz Highleyman](#)

Broadly neutralizing antibodies (bnAbs) may work well with lenacapavir or cabotegravir in long-acting regimens for HIV treatment, according to two presentations this week at the [Conference on Retroviruses and Opportunistic Infections \(CROI 2025\)](#) in San Francisco.

One study showed that teropavimab and zinlirvimab, two bnAbs from Gilead Sciences, worked well in combination with twice-yearly lenacapavir (Sunlenca). The other showed that N6LS, a bnAb from ViiV Healthcare, is a potential partner for long-acting cabotegravir.

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 of individuals naturally make broadly neutralizing antibodies that target conserved parts of the virus that don't change much. These specialized antibodies are being explored for HIV [prevention](#), [treatment](#) and [functional cure](#), but the virus can develop resistance to bnAbs, so they are best used in combination therapy.

Lenacapavir Plus Two bnAbs

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

[Lenacapavir](#), the first HIV capsid inhibitor, is administered by injection every six months. It is approved in combination with other antiretrovirals for highly treatment-experienced people with multidrug-resistant HIV, but it currently does not have equally durable partners to build a complete twice-yearly regimen; bnAbs could potentially fill this role.

Teropavimab (GS-5423) is derived from a bnAb called 3BNC117 that targets the CD4 binding site, which the virus uses to enter cells. Zinlirvimab (GS-2872) is derived from 10-1074, a bnAb that binds to the V3 loop on HIV's surface. Both bnAbs were modified to extend their half-life in the body 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, while more than 90% is sensitive to at least one.

[At CROI 2023](#) and in [The Lancet HIV](#), researchers reported results from a small Phase I trial showing that the triple combination—dubbed LTZ—maintained viral suppression for six months in people highly susceptible to both bnAbs. Further data reported at [CROI 2024](#) and at the [Glasgow HIV Drug Therapy meeting](#) last fall showed that the combination could be effective for people who were highly sensitive to at least one of the antibodies if they received high enough doses. Those results underscore the importance of screening for viral sensitivity prior to treatment.

These findings set the stage for the Phase II study, which enrolled 80 participants who were highly susceptible to both teropavimab and zinlirvimab according to a phenotypic resistance assay. They had undetectable viral load (below 50 copies) on a standard daily oral antiretroviral regimen for at least a year.

Compared with the Phase I trial, this study enrolled a more diverse population. Although most (85%) were men, more than a third were Black and a quarter were Latino. The median age was approximately 51 years. They had well-preserved immune function with a mean baseline CD4 count of 749.

After antibody sensitivity screening, 53 people were randomly assigned to switch to lenacapavir plus the two bnAbs while 27 stayed on their daily oral regimen. The group that switched received a loading dose of oral lenacapavir on the first two days, subcutaneous injections of lenacapavir every six months and intravenous infusions of teropavimab (2,550 mg) and zinlirvimab (2,550 mg) every six months. These fixed doses are comparable to the optimal weight-based doses in the Phase I study.

The response rate was high overall: 96% of people in both treatment groups maintained viral suppression at week 26. Lenacapavir, teropavimab and zinlirvimab remained well above therapeutic levels over time. Average CD4 counts increased, with no significant difference between the two groups.

One person in the LTZ group experienced virological failure. This individual had a viral blip at week 12 and higher viral rebound around week 24, after which they resumed Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine) and regained viral suppression. While this participant maintained average levels of the two bnAbs, the lenacapavir concentration fell below the mean. The person showed resistance to lenacapavir (Q67H mutation) and loss of sensitivity to zinlirvimab at 24 weeks.

The LTZ regimen was safe and generally well tolerated with no severe drug-related adverse events, serious treatment-emergent adverse events or withdrawals due to adverse events. The most common side effect in this group was mild lenacapavir injection site reactions (ISRs); pain and other reactions were less common and usually mild. No one experienced infusion-related reactions to teropavimab or zinlirvimab.

“We believe that the high efficacy of viral suppression and the safety data support continuing our study and support the clinical development of what we think is an exciting six-monthly HIV regimen,” Ogbuagu told reporters at a conference media briefing. The twice-yearly lenacapavir, teropavimab and zinlirvimab combination is “the longest-acting complete regimen in advanced development,” he said. “The beauty of it is that they can all just be administered together,” which would improve the logistics of therapy.

This study is ongoing with plans for an extension to 52 weeks. Earlier this year, the U.S. Food and Drug administration granted the LTZ regimen a Breakthrough Therapy Designation, intended to speed development of new drugs that may demonstrate substantial improvement over available therapy.

Cabotegravir Plus One bnAb

In the second study, Babafemi Taiwo, MBBS, of ViiV Healthcare, and colleagues evaluated the safety, efficacy and tolerability of long-acting cabotegravir plus N6LS. [Injectable cabotegravir and rilpivirine \(Cabenuva\)](#), administered by injection once monthly or every other month, is currently the longest-acting approved complete antiretroviral regimen.

N6LS (also known as VH3810109) targets the gp120 protein on HIV’s surface, which the virus uses to bind to CD4 cells. In the previous Phase I SPAN study, ViiV researchers showed that N6LS had a favorable safety profile in HIV-negative adults when given by either intravenous infusion (60 mg/kg) or by subcutaneous injection (3,000 mg) in combination with hyaluronidase, an enzyme that aids absorption and enables higher dosing.

The Phase IIa BANNER study found that a single IV infusion or subcutaneous injection of N6LS substantially reduced viral load in HIV-positive people who had not yet started antiretroviral treatment. But like other single agents, the bnAb alone does not maintain viral suppression for long. The Phase IIb EMBRACE trial ([NCT05996471](#)) therefore combined N6LS with long-acting cabotegravir.

EMBRACE, conducted at 45 sites in the United States and Puerto Rico, enrolled 125 HIV-positive adults with viral suppression (below 50 copies) for a year who were screened to ensure that they were sensitive to N6LS. They had no prior history of virological failure, had a CD4 count of at least 350 and did not have hepatitis B. More than 80% were men, 63% were white, 28% were Black, about 40% were Latino and the median age was 53 years.

The study participants were randomly assigned to receive injectable cabotegravir every month plus N6LS given by either IV infusion or subcutaneous injection every four months, using the same doses as SPAN, or to stay on their current standard oral regimen.

After six months, 96% of people randomized to N6LS infusions and 88% of those who received N6LS injections maintained viral suppression, as did 96% of those who stayed on their oral regimen.

Two people in each N6LS group—but no one in the standard-of-care group—experienced confirmed virological failure, defined as two consecutive viral load measurements of 200 or higher. All regained viral suppression when they resumed oral treatment. The two who received infusions had evidence of reduced sensitivity to N6LS but no integrase resistance mutations, while the two who received injections did not show N6LS resistance; one had an integrase resistance mutation (Q148R).

N6LS was safe when given by either IV infusion or subcutaneous injection, with no drug-related serious adverse events, but the infusions were better tolerated. Four infusion recipients (8%) experienced infusion site reactions, such as pain or redness, all of them mild. In contrast, 25 injection recipients (51%) experienced ISRs, ranging from mild to severe. What's more, these reactions lasted longer with injections compared with infusions, in some cases up to two weeks. However, no one in either group discontinued treatment due to ISRs.

"N6LS administered IV or subcutaneous every four months in combination with monthly [long-acting cabotegravir] maintained viral suppression in a high proportion of adults with baseline N6LS sensitivity," Taiwo and colleagues concluded.

ViiV considers these findings promising enough to advance the combination to the second part of the study, which will evaluate long-acting cabotegravir given every two month plus N6LS given every six months using the IV infusion formulation.

Comparing the two regimens, Gilead's triple combination would offer a complete twice-yearly regimen, which would be more convenient for patients and logistically simpler for providers. Gilead is now working on a [once-yearly formulation of lenacapavir](#), which looks promising for pre-exposure prophylaxis (PrEP) and could potentially also be used for treatment. If twice-yearly N6LS proves effective, it might be partnered with experimental ultra-long-acting formulations of cabotegravir that could be [given every four months](#) or less. Administering bnAbs by infusion involves more complex logistics than injections, but this may be feasible if they only need to be given twice a year.

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