Long-Acting Lenacapavir Shows Continued Promise

The injectable antiretroviral could potentially be given once every six months for HIV treatment or prevention.

February 22, 2022 By Liz Highleyman

UPDATE: On May 16, the Food and Drug Administration lifted its clinical hold on lenacapavir after Gilead Sciences switched to a different type of glass vial. Trials of lenacapavir for HIV treatment and prevention may now resume.

UPDATE: In late December, Gilead announced that the Food and Drug Administration had put a clinical hold on trials of lenacapavir due to concerns about the type of glass vial used for the injectable formulation. On March 1, the FDA issued a complete response letter for the New Drug Application for lenacapavir, citing manufacturing and control issues related to the borosilicate glass vials. Gilead said it intends to provide a plan, with corresponding data, to use a different vial type.

Lenacapavir, a long-acting HIV capsid inhibitor, continues to show good viral suppression, both for people starting antiretroviral treatment for the first time and for treatment-experienced people with multidrug-resistant virus, according to studies presented at the Conference on Retroviruses and Opportunistic Infections 2022 (CROI 2022).

Lenacapavir (formerly known as GS-6207), from Gilead Sciences, disrupts the HIV capsid, the cone-shaped shell that surrounds the viral genetic material and essential enzymes. Laboratory studies have shown that it interferes with multiple stages of the HIV lifecycle. Because it works differently than existing drugs, it remains active against virus that has developed resistance to other antiretroviral classes. What's more, lenacapavir has a long half-life in the body and could potentially be used for long-acting treatment or pre-exposure prophylaxis (PrEP).

First-Line Treatment

The Phase II CALIBRATE trial is evaluating lenacapavir as a component of first-line treatment. The study enrolled 182 previously untreated people with HIV. The median age was 29 years, half were Black and 45% were Latino. Representation of women was low, at just 7%. All had a viral load of at least 200, including 15% with a high viral load above 100,000. The median CD4 count was 437 and no one fell below 200 cells.

The participants were split into four groups. After a two-week lead-in period on oral lenacapavir, two groups started subcutaneous injections of lenacapavir every six months plus daily oral tenofovir alafenamide/emtricitabine (the drugs in Descovy). At 28 weeks, 52 people dropped emtricitabine and continued on daily tenofovir alafenamide (TAF) for another six months (treatment group 1). Another group of 53 dropped TAF/emtricitabine and continued on the once-daily integrase inhibitor bictegravir (treatment group 2). A third group of 52 received daily lenacapavir tablets plus TAF/emtricitabine for a year (treatment group 3). Finally, a control group of 25 people received a year of standard therapy using daily oral Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine).

At last year's International AIDS Society Conference on HIV Science (IAS 2021), Samir Gupta, MD, of Indiana University presented the first findings from the study. At 28 weeks, 94% of those taking oral or injectable lenacapavir and everyone in the control group had an undetectable viral load (under 50).

At CROI, Gupta presented updated results at week 54. At that point, 90% of participants in treatment group 1 and 85% each in treatment groups 2 and 3 had a viral load below 50, as did 92% of those in the control group. Looking only at those who had viral suppression at week 28, the response rates in the four groups were 94%, 92%, 90% and 92%, respectively, with two people (4%) in group 1, none in group 2, three (6%) in group 3 and none in the control group having HIV RNA over 50.

Just six participants met the criteria for drug resistance testing. Of these, one each in treatment groups 2 and 3 showed evidence of emergent lenacapavir resistance mutations. In both cases, the pattern of emergent mutations or drug levels and pill counts pointed to poor adherence to TAF/emtricitabine, meaning lenacapavir was essentially working on its own.

Along with high rates of viral suppression, people in all four groups saw similar CD4 count increases: 206, 212, 220 and 193 cells, respectively.

Treatment with lenacapavir was generally safe and well tolerated. Pooling data from all three lenacapavir treatment groups, there were no serious or grade 4 adverse events or clinically relevant laboratory abnormalities. Up to 14% of people in treatment groups 1 and 2 experienced injection site reactions, such as swelling, redness, pain or nodules; in general, these were less common after the second lenacapavir shot. Pain and swelling were temporary, but nodules and induration (hardness at the injection site) lasted a median of about 200 days. Three people discontinued treatment due to injection site reactions.

These findings, Gupta concluded, support the ongoing evaluation of lenacapavir for HIV treatment and prevention.

Treatment-Experienced People

The Phase II/III CAPELLA trial is evaluating lenacapavir in heavily treatment-experienced individuals. This study enrolled 72 people with resistance to at least two drugs from three of the

four major antiretroviral classes. About 75% were men, 38% were Black and 21% were Latino. The median age was 52 years, they had been living with HIV for 24 years on average and they had tried a median of 11 drugs. They were currently on antiretroviral therapy but unable to maintain viral suppression. About two thirds had advanced immune suppression with a CD4 count below 200.

The first 36 participants were randomly assigned to add either oral lenacapavir or a placebo to their failing regimen for 14 days. During this period, lenacapavir was essentially functioning as monotherapy. At that point, everyone was offered lenacapavir injections every six months plus an optimized background regimen selected based on resistance testing. Another 36 people in a nonrandomized open-label cohort received injectable lenacapavir (starting with a 14-day oral lead-in period) plus an optimized background regimen from the outset.

At last year's CROI, researchers reported that at the end of the initial 14-day period, 88% of participants in the lenacapavir group experienced at least a 0.5-log drop in viral load, compared with just 17% in the placebo group, and those using lenacapavir saw a significantly greater mean change in viral load (-1.93 log versus -0.29 log). Among the 26 participants who received their second lenacapavir injection and were followed through 26 weeks, 73% achieved an undetectable viral load (below 50).

At IAS 2021, researchers presented follow-up results from the randomized cohort after more participants had received their second injection. In this analysis, 81% had a viral load below 50 and 89% had HIV RNA below 200 at 26 weeks.

A poster at this year's CROI provided updated results. At 26 weeks, 81% of people in the open-label cohort had a viral load below 50 and 86% fell below 200; 17% and 11%, respectively, experienced virological failure based on the two cut-offs.

At 52 weeks, 83% of participants in the randomized cohort had HIV RNA below 50 and 86% had a viral load under 200; 14% and 11%, respectively, experienced virological failure and one person was missing viral load data. But response rates differed according to the number of active drugs in a person's background regimen. Among those with two or more active agents, 94% reached a viral load below 50, compared with 79% of those with just one active drug and 67% of those with none.

Among the 21 people who met the criteria for resistance testing, eight showed evidence of emerging lenacapavir resistance (two each in the randomized and open-label cohorts). All eight were at high risk for resistance, having either no active background drugs or inadequate adherence to the background regimen. All of them stayed on lenacapavir and three regained viral suppression at a later visit, including two who did not change their background regimen.

The mean CD4 increase in the randomized cohort was 83 cells at 52 weeks. Over time, the proportion of people with a very low CD4 count (below 50) fell from 22% to 3%, while the proportion with an adequate count (200 or higher) steadily rose, from 25% to 60%. In the open-label cohort, the mean increase was 98 cells at 26 weeks.

Again, lenacapavir was generally safe and well tolerated with no drug-related serious adverse events. Injection-site reactions were similar to those seen in the CALIBRATE trial. Most were mild to moderate and transient, but some participants experienced prolonged nodules or induration, and one person discontinued treatment for this reason.

Findings from these two studies show that lenacapavir has the potential to be used as a component of a long-acting treatment regimen, but there are currently no other antiretrovirals that can be given at such a long interval.

The approved regimen with the longest duration, Cabenuva (injectable cabotegravir and rilpivirine), is administered monthly or every two months. Islatravir, Merck's experimental nucleoside reverse transcriptase translocation inhibitor, has a long half-life and has shown promise for long-acting HIV treatment and prevention (including an implant that maintains drug levels for a year); however, islatravir trials were put on hold last year due to unexplained side effects. In addition, Gilead has licensed a set of broadly neutralizing antibodies that could potentially be used for long-acting HIV treatment.

Long-acting PrEP is a different story, because a single drug is enough to prevent HIV infection on its own. Studies of twice-yearly lenacapavir injections for PrEP are currently underway.

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