Twice-Yearly Lenacapavir Works Well for People with Highly Resistant HIV

The novel HIV capsid inhibitor also shows promise for previously untreated people.

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Lenacapavir, the first HIV capsid inhibitor, led to viral suppression in 81% of people who had used several prior antiretroviral medications and had multidrug-resistant virus, according to a presentation at the 11th International AIDS Society Conference on HIV Science. Another study found that the twice-yearly drug also shows promise for people starting treatment for the first time.

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. Previous laboratory research showed that lenacapavir interrupts multiple stages of the HIV lifecycle. Because it works differently than existing antiretrovirals, it has the potential to remain active against virus that has developed resistance to other types of drugs.

Early clinical trials showed that a single injection of lenacapavir as monotherapy led to substantial reduction in viral load, and the drug appears to have a high barrier to resistance. A study presented at this year's Conference on Retroviruses and Opportunistic Infections showed that oral lenacapavir led to rapid viral load reduction in highly treatment-experienced people. Gilead recently requested Food and Drug Administration approval of lenacapavir for treatment-experienced people with limited treatment options.

Treatent-Experienced People

Jean-Michel Molina, MD, PhD, of Hôpital Saint Louis in Paris, presented the latest findings from the ongoing Phase II/III CAPELLA trial, which is evaluating lenacapavir for people with highly resistant HIV whose current antiretroviral therapy is not working.

"Despite the advances in treating HIV infection, there remains an unmet need for treatment options for people who struggle with multi-drug resistance," Molina said in a Gilead press release. "As a physician, it's frustrating to have limited options for these patients who are at greater risk of progressing to AIDS."

In the functional monotherapy part of the trial, 36 adults with resistance to multiple antiretroviral drug classes who had a detectable viral load on their current regimen were randomly assigned to

add oral lenacapavir or a placebo to their failing regimen for 14 days. As previously reported, 88% of those assigned to lenacapavir had at least a half-log reduction in viral load at that point, compared with just 17% in the placebo group.

In the maintenance part of the study, all participants receive subcutaneous injections of lenacapavir every six months for a year plus an optimized background regimen designed to work as well as possible based on resistance testing. A second nonrandomized open-label cohort includes another 36 people who received oral lenacapavir for 14 days followed by injections every six months plus an optimized background regimen.

In the two groups combined, 75% are men, and the median age is 52 years. They were diagnosed with HIV a median of 24 years ago, had tried a median of 11 prior antiretrovirals and nearly two thirds have advanced immune suppression with a CD4 count below 200. Almost all have HIV that is resistant to nucleoside/nucleotide reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors, 81% are resistant to protease inhibitors and 69% are resistant to the newer integrase inhibitors.

Molina presented 26-week efficacy data for the randomized cohort and safety data for both the randomized and open-label cohorts. At that point, all of the 36 randomized participants and three of the 36 open-label participants had received a second injection of lenacapavir.

At 26 weeks, 81% of participants in the randomized cohort had an undetectable viral load below 50 while 89% had a viral load less than 200. People who had no fully active drugs in their optimized background regimen didn't fare as well, with 67% achieving an undetectable viral load. But it is still quite an achievement for four out of six people with highly resistant HIV to achieve viral suppression on lenacapavir functional monotherapy.

Viral suppression was accompanied by CD4 cell recovery, with an average gain of 81 cells. The proportion of participants with a very low CD4 count below 50 dropped from 22% at baseline to zero at week 26.

Among the 11 participants who met the criteria for resistance testing, four showed evidence of emergent lenacapavir resistance mutations, including M66I, Q67H, K70N/R/S and N74D. All four stayed on lenacapavir, and three experienced viral resuppression, including two who did not change their background regimen. No one developed further resistance to the drugs in their background regimen.

Lenacapavir was generally safe and well tolerated. No drug-related serious adverse events were reported, and no one stopped treatment early due to adverse events. The most common non-injection-related side effects were diarrhea and nausea, each reported by 8% of participants. About a quarter experienced severe lab abnormalities, but none were deemed clinically relevant. Injection site reactions were more common, including swelling (26%), redness (24%), pain (19%) and nodules (18%). But most reactions were mild and resolved with a few days, and no one stopped treatment for this reason.

“Lenacapavir had the potential to become an important agent for heavily treatment-experienced people with HIV with multidrug resistance,” the researchers concluded.

“The CAPELLA results are exciting as they demonstrate that an undetectable viral load is achievable in a patient population that has typically had challenges with viral suppression over the course of their journey living with HIV,” Molina said. “New, long-acting options in development, like lenacapavir, are critical to changing the clinical landscape, and I’m encouraged that lenacapavir can potentially help improve clinical outcomes.”

First-Time Treatment

Lenacapavir is also being developed as a component of long-acting antiretroviral therapy for previously untreated people.

Samir Gupta, MD, of Indiana University School of Medicine, presented results from the ongoing Phase II CALIBRATE trial, which is evaluating lenacapavir as a twice-yearly option for first-time treatment.

The study enrolled 182 previously untreated participants with a viral load of at least 200 and a CD4 count of 200 or higher. The population is racially diverse, with half being Black and 45% Latino, but only 7% are cisgender women. About one in six started with a high viral load above 100,000, and the median CD4 count was 437.

During the induction part of the study, participants were randomly assigned to receive a subcutaneous injection of lenacapavir plus daily oral Descovy (tenofovir alafenamide/emtricitabine) after a two-week oral lead-in; daily oral lenacapavir plus Descovy; or daily oral Biktarvy (bictegravir/tenofovir alafenamide/emtricitabine) for 28 weeks. During the maintenance part, those who received lenacapavir injections were randomized to receive daily oral tenofovir alafenamide (sold as Vemlidy for hepatitis B) or bictegravir and will continue to receive lenacapavir injections every six months.

At 28 weeks, 94% of people receiving injectable lenacapavir to be followed by tenofovir alafenamide and 92% of those who received injectable lenacapavir to be followed by bictegravir had an undetectable viral load below 50, as did 94% of those on daily oral lenacapavir plus Descovy and 100% of those on daily Biktarvy.

One person in the second treatment group, who started with a high viral load, did not achieve viral suppression and had evidence of emergent drug resistance mutations that reduced lenacapavir sensitivity, although their lenacapavir levels remained within the target range. Sixteen others who did not have viral suppression in the intention-to-treat analysis had missing viral load data. Gupta noted that if these people turn out to have viral suppression with further follow-up, the combined efficacy of lenacapavir would rise to 99%.

Here too, treatment was safe and well-tolerated, with no serious or severe drug-related adverse

events. Most adverse events and laboratory abnormalities were similar in the combined lenacapavir arms and the Biktarvy group. Nausea was more common among people taking injectable versus oral lenacapavir (12% versus 8%) but diarrhea was less common (6% versus 8%). Just over a third (39%) of injectable lenacapavir recipients reported injection site reactions, which again were mostly mild and resolved within days; only two people stopped treatment for this reason.

The researchers concluded that these data support the ongoing evaluation of lenacapavir for the treatment and prevention of HIV.

However, using lenacapavir in a combination regimen for HIV treatment presents a challenge, as there are currently no other antiretrovirals that can be given at such long intervals. An islatravir implant that maintains drug levels for a year could offer one option, and Gilead is testing broadly neutralizing antibodies that could potentially be paired with lenacapavir for long-acting treatment.

Lenacapavir is being studied for pre-exposure prophylaxis (PrEP) as well, and a single drug may be enough to prevent HIV. Lenacapavir injections administered every six months will be evaluated in the Women's HIV Prevention Study, which is also comparing Truvada (tenofovir disoproxil fumarate/emtricitabine) and Descovy (tenofovir alafenamide/emtricitabine) for adolescent girls and young women in sub-Saharan Africa, and in another study of cisgender men, transgender women and trans men who have sex with men in the United States and South Africa.

Click here to read the treatment-experienced study abstract.
Click here to read the treatment-naive study abstract.
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