New Long-Acting Integrase and Capsid Inhibitor Are on the Horizon

With encouraging data for oral formulations of VH-184 and VH-499, long-acting injectables are now being evaluated.

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Two new HIV antiretrovirals with a high barrier to resistance—a next-generation integrase inhibitor and a capsid inhibitor from ViiV Healthcare—look promising in early studies presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2025) this month in San Francisco.

Oral versions of VH4524184 (VH-184 for short), the novel integrase inhibitor, and VH4011499 (VH-499), the capsid inhibitor, both demonstrated strong antiviral activity and good safety profiles, laying the groundwork for the development of long-acting injectable formulations.

Modern antiretroviral therapy is generally highly effective and well tolerated, but new long-acting options are still needed. Some people have difficulty maintaining good adherence to daily oral treatment because they forget to take their pills, don't want to think about HIV every day or are in living situations where their meds could be lost or stolen. The current longest-acting regimen, ViiV's Cabenuva (injectable cabotegravir and rilpivirine), requires administration by a health care provider monthly or every other month.

"It's clear long-acting injectable medicines deliver on unmet patient need and will play a critical role in achieving our ambition of ending HIV and AIDS," Kimberly Smith, MD, MPH, ViiV's head of research & development, said in a news release. "Data shows that the potency and tolerability of our third-generation [integrase inhibitor] and our capsid inhibitor will make them a major part in the development of our next generation of long-acting injectable therapies."

VH-184

VH-184 is a third-generation integrase inhibitor with a higher barrier to resistance and activity against many viral strains that have developed resistance to earlier drugs in this class, such as ViiV's widely used dolutegravir and Gilead Sciences' bictegravir (a component of the Biktarvy combination pill).

Luise Rogg, MD, PhD, of ViiV and colleagues conducted a Phase IIa proof-of-concept trial to

evaluate various doses of VH-184 in people living with HIV in North America, Argentina and Europe. The study included 22 participants who were starting antiretroviral treatment for the first time. Nearly 90% were men, 68% were white, 14% were Black and 59% were of Latino ethnicity and the median age was 32 years. At baseline, they had a viral load of 3,000 copies or more and a CD4 T-cell count of at least 200.

The participants were randomly assigned to receive oral VH-184 as a single agent at doses of 10, 50 or 300 milligrams, or a placebo, every three days (that is, on Days 1, 4 and 7). After the 10-day monotherapy period, they started a standard combination antiretroviral regimen.

VH-184 demonstrated "robust antiviral activity," Rogg reported. Blood plasma viral load declined from baseline through Day 10 with all VH-184 doses, but there was no change in the placebo group. The mean maximum changes in HIV RNA ranged from −1.17 to −2.31 log copies. Of note, the maximum viral load reduction was similar to that seen in early studies of dolutegravir monotherapy. No genotypic or phenotypic drug resistance mutations were detected at the end of the monotherapy period.

Treatment was safe and well tolerated. Two VH-184 recipients reported mild to moderate vomiting. There were no serious adverse events or withdrawals due to side effects. No clinically relevant changes in laboratory parameters, electrocardiograms or vital signs were observed.

"The third-generation [integrase inhibitor], VH-184, which has a potentially higher barrier to resistance than second-generation [integrase inhibitors], demonstrated rapid and highly potent antiviral activity in people with HIV-1," the researchers concluded.

VH-499

At the same conference session, Paul Benn, MB, ChB, of ViiV, presented findings from another Phase IIa proof-of-concept trial evaluating the capsid inhibitor VH-499. Prior studies showed that resistance is likely to be rare and it has a low potential for drug-drug interactions, according to Benn.

There is currently only one approved HIV capsid inhibitor, Gilead's lenacapavir (Sunlenca). It is given by subcutaneous injection once every six months as part of a combination regimen for people with multidrug-resistant virus; it also works well alone for pre-exposure prophylaxis (PrEP).

Similar to the VH-184 study, this trial included 23 previously untreated people with HIV in north America, Argentina, Europe and the United Kingdom. Most (83%) were men, 65% were white, 17% were Black, 65% were Latino and the median age was 31. At baseline, they had a viral load of at least 3,000 copies and a CD4 count of at least 200.

The participants were randomly assigned to receive oral VH-499 alone at doses of 25, 100 or 250 mg, or a placebo, every five days (on Days 1 and 6). After the 10-day monotherapy period, they started standard antiretroviral therapy.

Here too, VH-499 demonstrated “highly potent antiviral activity,” Benn reported. Plasma viral load declined from baseline through Day 11 in all dose groups, with the largest mean maximum change seen with the 250 mg dose (−2.17 log copies). Increasing VH-499 exposure was associated with greater viral load decline. One person taking the lowest dose of VH-499 developed a single emergent mutation associated with reduced sensitivity to capsid inhibitors (Q67Q/H) but was able to achieve viral suppression after starting oral dolutegravir and lamivudine.

VH-499 was also safe and well tolerated with mild to moderate side effects, no relevant changes in clinical lab parameters, electrocardiograms or vital signs, no serious adverse events and no withdrawals due to adverse events.

“The new HIV-1 capsid inhibitor VH-499 demonstrated highly potent antiviral activity in people with HIV-1, with up to a mean maximum 2.2 log copies/mL reduction in HIV-1 RNA,” the researchers concluded.

Long-Acting Treatment

Antiretroviral studies often start with oral dosing to establish their activity—and new oral meds that work against resistant virus are always welcome—but long-acting injectables are the goal for both HIV treatment and prevention.

“The question I often get is, ‘Why do we need another [integrase inhibitor] when the ones we have now are very good?’” Rogg said at a CROI media briefing. “What I can tell people is that adherence is hard. It is hard to take medication every day for the rest of your life. I want to be able to bring the power of a [integrase inhibitor] in a long-acting formulation.”

Ongoing Phase I studies are evaluating the safety, tolerability and pharmacokinetics of subcutaneous and intramuscular injectable formulations of VH-184 (NCT06310551) and VH-499 (NCT06012136, NCT06724640) in healthy HIV-negative adults. If results are favorable, these would set the stage for trials of people living with HIV.

The VH-499 Phase IIa results are “really encouraging data” Benn told reporters. He noted that having long-acting agents with a low propensity for drug interactions is especially important for an aging HIV population with comorbidities who may be taking multiple other medications.

The maximum durations of VH-184 and VH-499 are not yet clear, as studies are working their way up. Ultimately, researchers hope for regimens that can be administered together every six months or less. Gilead has achieved twice-yearly dosing of lenacapavir—and once-yearly looks promising—but it currently does not have equally long-acting partners to build a complete regimen with such long duration. Depending on further data, VH-184 and VH-499 might be used together in combination regimens. Both ViiV and Gilead are working on broadly neutralizing antibodies that also could potentially be components of long-acting treatment.

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