Pipeline Drugs Could Allow for Twice-Yearly HIV Treatment

Early studies suggest VH-499, VH-184 and GS-3242 could be new building blocks for complete long-acting regimens.

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Three experimental injectable antiretrovirals—a novel capsid inhibitor and two next-generation integrase inhibitors—could be components of future long-acting HIV treatment regimens, according to study results presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2026) last week in Denver.

Pharmacokinetic data showed that ViiV Healthcare's investigational capsid inhibitor VH-499, ViiV's experimental integrase inhibitor VH-184 and Gilead Sciences' pipeline integrase inhibitor GS-3242 could potentially be administered by injection just twice a year. All three were safe and generally well tolerated, and Phase II studies are expected to start this year.

Modern antiretroviral therapy is 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 longest-acting approved regimen, ViiV's Cabenuva (injectable cabotegravir and rilpivirine), is administered by a health care provider monthly or every other month. Gilead Sciences' Sunlenca (lenacapavir) is administered twice yearly, but it currently has no equally long-acting partners to make up a complete regimen.

VH499

VH4011499 (VH-499 for short) could become the second approved HIV capsid inhibitor after lenacapavir. It is not an inhibitor or inducer of CYP3A4, an enzyme that metabolizes many drugs, suggesting it should have minimal drug interactions—an important consideration for people aging with HIV who may be taking multiple medications for other conditions.

At last year's CROI, researchers presented data from a small Phase IIa proof-of-concept study evaluating an oral formulation of VH-499 in people starting treatment for the first time. Antiretroviral studies often start with short-term oral dosing to establish a drug's safety and antiviral activity before moving on to long-acting injectable formulations. VH-499 administered

every five days demonstrated highly potent activity. The pills had a favorable safety profile with no serious adverse events or withdrawals due to side effects.

This set the stage for the first human trial of a long-acting injectable version of VH-499. Nilay Thakkar, PhD, a clinical pharmacologist at GSK, presented results at this year's conference.

This Phase I study (NCT06724640) enrolled 65 HIV-negative adults. A majority (60%) were men, the median age was 36 years, about half were white and about a third were Black. They were randomly assigned to receive a single injection of various doses of VH-499 (100, 200, 400 or 800 milligrams), administered by subcutaneous injection in the abdomen or intramuscular injection in the buttocks, or a matching placebo.

Injectable VH-499 was generally well tolerated. Overall, 87% of participants had at least one injection site reaction (ISR), mainly pain, but these were mostly mild, with a median duration of one to four days. Just two people in the subcutaneous injection group reported severe ISRs. Reactions were more common with VH-499 compared with the placebo, but they did not vary notably by dose. People who received the subcutaneous injections reported more ISRs, including nodules—caused by the drug forming a long-lasting depot under the skin—than those who received intramuscular shots. There were no serious non-ISR adverse events, and no one withdrew for this reason.

The pharmacokinetic profile of VH-499 supports twice-yearly dosing, Thakkar reported. Intramuscular injections had a half-life of about 11 weeks, and the drug is expected to rapidly reach effective concentrations within 48 hours. He noted that the half-life is longer with subcutaneous shots, but further follow-up is needed.

VH-184

VH4524184 (VH-184 for short) is a third-generation integrase inhibitor with a high barrier to resistance and activity against many HIV strains that have developed resistance to earlier drugs in this class.

As with VH-499, researchers presented data from a small Phase IIa study at last year's CROI, showing that an oral formulation of VH-184 taken every three days demonstrated robust antiviral activity with no emergent resistance mutations in people new to HIV treatment. It, too, was safe and well tolerated.

This year, Hyunmoon Back, PhD, also a clinical pharmacologist at GSK, presented results from the first human study of injectable formulations of VH-184. This Phase I study (NCT06310551) enrolled 76 HIV-negative adults. Approximately 90% were men, median ages ranged from 33 to 51 years and white and Black participants were well represented.

The participants were randomly assigned to receive a single injection of various doses of two formulations of VH-184, administered by subcutaneous injection or intramuscular injection in the thigh or buttocks, or a matching placebo.

Injectable VH-184 was also generally well tolerated. Overall, 80% of participants had at least one ISR, predominantly pain (68%), but these were usually mild, with a median duration of four to eight days. People randomized to Formulation A had more ISRs, including pain and itching, than those who received Formulation B. The frequency of most reactions did not differ much by dose, administration route or injection site, but nodules—usually not visible, Back noted—mostly occurred with subcutaneous shots. Non-ISR adverse events were uncommon, and no one withdrew from the study for this reason.

The pharmacokinetic profile supports the ultra-long-acting potential of VH-184, according to Back. Formulation B was not only better tolerated, but it also lasted longer, with a half-life ranging from 14.9 weeks for intramuscular thigh injections to 19.8 weeks for subcutaneous injections. Simulation modeling predicted that this formulation would maintain effective drug concentrations if given every four to six months, while Formulation A would likely require monthly or every-other-month dosing, like cabotegravir.

GS-3242

At the same session at CROI, Samir Gupta, MD, of Indiana University School of Medicine, presented results from early human trials of Gilead's investigational integrase inhibitor GS-3242.

An open-label Phase Ib study (NCT07001319) evaluated the antiviral activity, safety and pharmacokinetics of an oral formulation of GS-3242 in 20 adults with HIV (17 men and three women) who were either being treated for the first time or were new to long-acting therapy and integrase inhibitors and had been off antiretrovirals for treatment or pre-exposure prophylaxis for at least 12 weeks.

The participants received one of three oral doses of GS-3242 (175, 450 or 900 mg) as monotherapy on the first two days of the study, and their viral load was assessed at 11 days. GS-3242 demonstrated potent antiviral activity, Gupta reported. Participants in all three dose groups saw a steady decrease in viral load. The drop in the 900 mg groups was comparable to the decline seen with the Biktarvy combination pill, he noted.

Oral GS-3242 was safe and generally well tolerated, with no serious or severe adverse events or events leading to discontinuation. Only one treatment-related adverse event was reported, in the lowest dose group.

In addition, a long-acting injectable formulation of GS-3242 was tested in a Phase Ia study that enrolled 34 HIV-negative volunteers. They received a single dose (400, 800, 1200 or 2400 mg) of GS-3242 or a placebo, administered via intramuscular injection in the thigh.

About a third of study participants who received the two lower doses experienced ISRs, rising to nearly 90% for those who got the highest dose. The most common reaction was mild to moderate pain. Nodules were not reported. No one experienced severe adverse events.

The half-life of GS-3242 ranged from 50 to 76 days; interestingly, this was longest using the lowest

dose. The pharmacokinetic data support a dosing interval of at least four months, and additional study cohorts are evaluating a six-month interval, Gupta said.

Taken together, these studies suggest that complete long-acting injectable regimens are likely to be the future of HIV treatment.

VH-499 and VH-184 could potentially be combined with experimental ultra-long-acting formulations of cabotegravir or ViiV's broadly neutralizing antibody lotivibart (N6LS) in a twice-yearly regimen. GS-3242 could be partnered with lenacapavir or Gilead's broadly neutralizing antibodies teropavimab and zinlirvimab administered every six months. Gilead is now testing a promising once-yearly version of lenacapavir, so annual treatment may one day be possible.

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