What’s in the Pipeline for HIV?

Researchers are working on longer-acting therapies for HIV treatment.

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The evolution of HIV treatment is among the most remarkable success stories in medical history. From handfuls of pills taken multiple times a day to injections administered just twice a year, antiretroviral therapy has come a long way. Today’s HIV treatment regimens are highly effective and generally well tolerated. What’s more, most people can take a single once-daily pill—similar to taking a statin to manage high cholesterol.

But the quest for new longer-acting options continues. Some people have trouble maintaining good adherence to daily oral treatment because they forget to take their pills, don’t want to think about having HIV every day or are living in situations where their meds could be lost or stolen. And it’s not just about convenience. Given the Trump administration’s deep cuts to foreign aid funding, including PEPFAR (the President’s Emergency Plan for AIDS Relief), long-acting treatment could help stretch limited resources.

The current longest-acting complete HIV treatment, ViiV Healthcare’s Cabenuva (injectable cabotegravir and rilpivirine), is administered once monthly or every other month. Gilead Sciences’ capsid inhibitor, lenacapavir (Sunlenca), is given every six months, but it is only approved for heavily treatment-experienced people with highly resistant virus.

By the time this issue of POZ is published, lenacapavir is expected to be approved for twice-yearly pre-exposure prophylaxis (PrEP). But while a single antiretroviral is enough to prevent HIV, treatment requires a combination approach. Today, there are no equally durable meds to build a complete biannual regimen, but many candidates are in the pipeline.

Novel Antiretrovirals

When it comes to oral treatment, taking pills once weekly or monthly instead of every day would be more convenient.

Gilead and Merck are evaluating lenacapavir pills plus islatravir, the first nucleoside reverse transcriptase translocation inhibitor, as a once-weekly oral regimen. Phase II results presented at IDWeek showed that 94% of people who switched from standard daily treatment to the weekly combo maintained an undetectable viral load. A fixed-dose combination pill is now being tested in Phase III trials.

Gilead is also testing a once-weekly integrase inhibitor (GS-1720) plus a pro-drug of lenacapavir (GS-4182) in Phase II studies as well as potential once-monthly oral integrase inhibitors and a monthly lenacapavir pro-drug (GS-3107) in Phase I. Pro-drugs—precursors that are converted to an active drug in the body—can improve oral bioavailability, allowing for lower doses and smaller pills.

Oral medications have inherent limitations to their durability, however, so treatment that works for months will likely continue to require shots. As potential twice-yearly partners for lenacapavir, Gilead is looking at two long-acting injectable integrase inhibitors (GS-1219 and GS-3242) and an islatravir pro-drug (GS-1614).

ViiV, too, is working on longer-acting candidates. At the Conference on Retroviruses and Opportunistic Infections (CROI) in March, researchers presented early data on oral versions of a third-generation integrase inhibitor (VH-184) and an experimental capsid inhibitor (VH-499). Both drugs demonstrated potent antiviral activity and a high barrier to resistance. This laid the groundwork for Phase I trials of long-acting injectable formulations of VH-184 and VH-499, with the goal of a complete regimen that can be administered every six months or less.

“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,” says Kimberly Smith, MD, MPH, ViiV’s head of research and development.

Broadly Neutralizing Antibodies

Looking beyond antiretrovirals, researchers are also exploring broadly neutralizing antibodies (bnAbs) for HIV prevention, treatment and functional cure.

People with HIV normally produce antibodies, but these mostly target parts of the virus that are hidden or highly variable. However, a small proportion of individuals make more potent antibodies that bind to conserved parts of the virus. Therapies derived from these natural bnAbs have been enhanced to improve their bioavailability.

Gilead is studying a pair of bnAbs, teropavimab (GS-5423) and zinlirvimab (GS-2872), as potential partners for injectable lenacapavir. Teropavimab is derived from a natural bnAb called 3BNC117 that targets the CD4 binding site, while zinlirvimab is derived from 10-1074, a bnAb that binds to the V3 loop on HIV's surface.

At CROI, Onyema Ogbuagu, MBBCh, of Yale University, presented findings from a Phase II trial of lenacapavir, teropavimab and zinlirvimab—dubbed LTZ—for people with viral suppression on daily oral treatment. After testing to ensure sensitivity to both bnAbs, 53 people were randomly assigned to switch to LTZ, receiving subcutaneous injections of lenacapavir and IV infusions of teropavimab and zinlirvimab every six months, while 27 stayed on their daily regimen. At 26 weeks, 96% of participants in both groups maintained viral suppression. LTZ was safe and well tolerated with no severe drug-related adverse events.

"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 said. "The beauty of it is that they can all just be administered together."

In another bnAb study, Babafemi Taiwo, MD, of ViiV, and colleagues evaluated long-acting cabotegravir plus N6LS (also known as VH3810109), an antibody that targets the gp120 protein on HIV's surface.

A previous analysis showed that a single IV infusion or subcutaneous injection of N6LS substantially reduced viral load, but the bnAb alone did not maintain viral suppression for long, so the Phase II EMBRACE trial combined it with cabotegravir. The study enrolled 125 people with viral suppression who were screened for sensitivity to N6LS. They were randomized to stay on their current regimen or switch to injectable cabotegravir every month plus N6LS infusions or injections every four months.

After six months, 96% of people randomized to N6LS infusions and 88% of those on N6LS injections maintained viral suppression. The bnAb was safe when administered by either route, but the infusions were better tolerated. The study is now evaluating cabotegravir every other month plus N6LS infusions every six months. In the future, N6LS might be paired with experimental ultra–long-acting formulations of cabotegravir or perhaps with VH-184 or VH-499.

Two other studies at CROI evaluated whether bnAbs can maintain viral suppression without antiretrovirals. In the RIO trial, which enrolled men in Europe, 75% of those who received infusions of the antibodies 3BNC117-LS and 10-1074-LS did not experience viral rebound five months after

stopping standard antiretroviral therapy, and a third were still in remission at 18 months. In the FRESH study, which enrolled women in Africa, 30% of those who received two other bnAbs, VRC07-523-LS and CAP256V2-LS, plus the immune-modulating drug vesatolimod maintained viral suppression for a year, including four who remained off antiretrovirals for more than two years.

The ultimate goal in the HIV field is a cure, but research has proceeded slowly with many disappointments. What's more, future advances in HIV basic science are threatened by reduced federal funding through the National Institutes of Health—the largest supporter of HIV and AIDS research worldwide. While researchers and advocates aren't giving up on a cure, people living with HIV can look forward to better treatment options on the horizon. Viral eradication may not be possible, but twice-yearly therapy is approaching long-term remission, or a functional cure.

While advances in treatment are not as dramatic as a one-and-done cure, a look back at history shows how far we've come, according to Joseph Eron, MD, of the University of North Carolina at Chapel Hill, lead investigator of the LTZ trial.

"We've gone from asking patients to wake up every four hours to take zidovudine [AZT], to combination treatment with 15 to 20 pills a day, to now having the opportunity to give therapy every six months," he says.
