Longer-Lasting HIV Meds Are on the Horizon

An extended-release formulation of tenofovir, lamivudine and dolutegravir maintained effective drug levels for a month.

December 26, 2023 By Liz Highleyman

HIV treatment has come a long way over the past four decades—from handfuls of pills taken multiple times a day to once-daily single-tablet regimens and injections every two months. Daily pills and every-other-month injections also prevent HIV acquisition. But longer-lasting options are still needed, as only about two thirds of people diagnosed with HIV in the United States have achieved viral suppression, and only one third of eligible individuals are on pre-exposure prophylaxis (PrEP).

Long-acting treatment and prevention are more convenient, more discreet and encourage good adherence. Research holds promise for therapies that can be taken even less often, and long-term remission is a goal on the horizon.

Currently, the longest-acting complete HIV treatment regimen is Cabenuva (injectable cabotegravir and rilpivirine), which is administered by a health care provider every one or two months. It is now approved only for people with an undetectable viral load who wish to switch to a new regimen, but recent pilot studies show that it can also work well for people without viral suppression. For HIV prevention, Apretude (injectable cabotegravir alone) works even better than PrEP pills.

Last December, the Food and Drug Administration approved Sunlenca (lenacapavir), the first HIV capsid inhibitor, which is administered every six months. So far, it is available only for treatment-experienced people with multidrug-resistant HIV, but it is also works well for initial treatment, and it is being studied for PrEP. Sunlenca is the longest-acting approved antiretroviral, but it can't be used alone, and it lacks an equally durable partner. In an effort to fill that gap, Gilead Sciences is now testing Sunlenca in combination with two broadly neutralizing antibodies as a complete twice-yearly regimen.

Long-Acting TLD

Further back in the pipeline, researchers are exploring other long-acting therapies. A team at the University of Washington in Seattle is testing an extended-release injectable formulation of

tenofovir disoproxil fumarate, lamivudine and the integrase inhibitor dolutegravir (sold alone as Tivicay). A daily oral combination of these three drugs—sometimes called TLD—is the most widely prescribed antiretroviral regimen worldwide.

As described in the journal AIDS, Simone Perazzolo, PhD, and colleagues used novel drug combination nanoparticle technology, which makes it possible to combine water-soluble and insoluble agents, to produce antiretrovirals that require less frequent administration. Despite the drugs' disparate physical and chemical properties, the researchers were able to stabilize and assemble tenofovir, lamivudine and dolutegravir into a formulation suitable for subcutaneous injection, which they dubbed TLD-in-DcNP.

Unlike some other long-acting medications that form a "depot" that releases drugs slowly over time, the TLD-in-DcNP agents are rapidly and completely absorbed by the lymphatic system, with no significant retention at the injection site, according to the researchers.

When TLD-in-DcNP was given to monkeys in an early study, all three antiretrovirals exhibited long-acting profiles, compared with the same drugs dissolved in liquid but not formulated into nanoparticles. Drug levels above predicted effective concentrations were maintained in blood plasma for four weeks after a single injection. Drug exposure levels were even higher in cells than in plasma, suggesting cell-targeted drug combination delivery, according to the researchers.

Tenofovir and lamivudine are also active against hepatitis B virus (HBV), making this regimen suitable for people with HIV/HBV coinfection. There are currently no long-acting treatment options for hepatitis B. What's more, the subcutaneous formulation, injected under the skin, might allow for self-administration, as opposed to intramuscular injections that must be administered by a health care provider.

The current TLD-in-DcNP formulation would have to be administered every month—compared with every other month for Cabenuva—but the drugs reach their maximum concentrations within one day, compared with about a week for cabotegravir and rilpivirine. Although injectable therapies can present logistical challenges, a long-acting regimen of familiar, well-tolerated drugs with low production cost could facilitate access in low- and middle-income countries.

"The successful transformation of short-acting to long-acting TLD-in-DcNP may provide an all-in-one long-acting first-line complete HIV treatment," the study authors concluded. "With dose adjustments, this novel all-in-one three HIV drug formulation opens new possibilities for long-acting HIV therapy, potentially transforming the lives of people living with HIV and HIV/HBV."

Lamivudine Hydrogel

Another research team, at Johns Hopkins University, is developing a hydrogel formulation of lamivudine. Hydrogels have unique water-absorbing properties that give them a jellylike consistency. The scientists tweaked lamivudine into a polymer, or large chain of molecules that can either stick together or come apart, depending on temperature, pH and other conditions. After injection, the solution self-assembles into a gel that stays close to the site of injection and slowly

releases the drug over six weeks.

As described in the Journal of the American Chemical Society, Honggang Cui, PhD, and colleagues injected the lamivudine hydrogel into the backs of mice. A single injection maintained effective drug concentrations for 42 days in plasma—and even longer in tissues such as the lymph nodes, liver and kidneys—while lamivudine injected without the hydrogel was undetectable within three days.

“Keeping the high drug levels in plasma for 42 days is very impressive. But in the future, we hope it will be even longer,” Cui said in a news release. The researchers think an optimized formulation might be able to achieve dosing intervals of several months or even longer.

Cui noted that the hydrogel injection consists entirely of the therapeutic agent itself, which could streamline regulatory approval. His team plans to test the technology with other medications, and it might be suitable for PrEP as well as HIV and hepatitis B treatment.

“This is a novel way to deliver anti-HIV meds, and this platform has the advantage that a single polymer can be programmed to deliver several different drugs simultaneously,” said study coauthor Charles Flexner, MD. “One of the drawbacks of the approved injectable HIV treatments is that none have activity against hepatitis B virus, which is a common coinfection with HIV, especially in Asia and Africa. This formulation delivers lamivudine, a drug active against both HIV and HBV, but can also be modified to deliver tenofovir, which is the current standard of care for HBV treatment.”

Even longer-lasting technologies for HIV treatment and prevention are in development. As reported at this year’s Conference on Retroviruses and Opportunistic Infections, researchers are testing small implants inserted under the skin that work like long-acting contraception. One team tested a refillable implant containing islatravir, Merck’s experimental nucleoside reverse transcriptase translocation inhibitor, that could last for several years, while another evaluated a biodegradable implant. Both implants protected female monkeys against vaginal infection with an HIV-like virus, and the refillable implant also protected male monkeys from rectal infection.

Click here for more news about HIV treatment.

Click here for more news about HIV prevention.
