Going Long

Long-acting therapies are the future of HIV treatment and prevention.

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From handfuls of pills taken multiple times a day to injections administered every other month, antiretroviral therapy has come a long way. HIV treatment is now more effective, better tolerated and much more convenient, which promotes good adherence. What's more, long-acting pre-exposure prophylaxis (PrEP) offers even better protection than daily pills.

"Long-acting injectables are a significant advance that offers important additional options for treatment of people with HIV and prevention in those who are candidates for PrEP," Daniel Kuritzkes, MD, of Brigham and Women's Hospital, told POZ. "It is likely that future advances will allow even less frequent dosing than the current monthly or every-other-month dosing now required, perhaps reducing dosing to just once or twice a year."

Daniel KuritzkesCourtesy of Brigham and Women's Hospital

Studies have shown that people who switch from daily oral antiretrovirals to long-acting injectable treatment or PrEP report greater satisfaction. (See "I Stopped Taking My HIV Pills," page 20.) Some of the reasons for preferring periodic injections include not having to think about HIV treatment or prevention every day, not needing to remember to take daily pills, not carrying pills when away from home, less worry about medications being lost or stolen and not having pill bottles that could reveal one's HIV-positive status or risk for HIV.

"We often think stigma occurs in specific communities, but in the SOLAR study, which was predominantly white men, stigma and disclosure came up very strongly as reasons for taking long-acting treatment," says Chloe Orkin, MD, of Queen Mary University of London. "Even in 2023, in areas where there are Pride parades, people still feel stigma. People want to be released from the burden of daily oral therapy."

"Daily pill-taking for treatment is difficult, but for prevention, it's even harder," she adds. "There's been very poor uptake of PrEP among women. I think if it were not visible, it might be better accepted, as seen with long-acting reversible contraception being far more popular than pills.C

Long-acting treatment and prevention are potentially revolutionary, but cost and limited availability can throw up barriers. In addition, long-acting injectables currently cannot be self-administered, meaning people must visit a health care provider up to 12 times a year. Such barriers can be overcome, but to really change the game, equitable access is critical.

"It's important that long-acting therapy is available everywhere and it's not a treatment for some people and not for others," Orkin says. "Continued efforts are needed to make sure this is universally available. In terms of PrEP, it's important that things move quickly in all countries."

What's Available Now?

Cabenuva (injectable cabotegravir and rilpivirine), from ViiV Healthcare and Janssen, is currently the only complete long-acting HIV treatment regimen. Approved by the Food and Drug Administration (FDA) in January 2021, it involves two intramuscular injections in the buttocks administered once monthly or every other month by a health care provider.

The ATLAS trial showed that people who switched from a standard oral regimen to monthly Cabenuva were as likely to maintain an undetectable viral load as those who stayed on daily pills. The ATLAS-2M study showed that participants who received the injections every eight weeks responded as well as those who did so every four weeks, with 94% in both groups maintaining viral suppression. A recent long-term follow-up analysis found that Cabenuva remained effective at three years. However, participants with virological failure in the every-other-month group were more likely to develop drug resistance than those in the once-monthly group, suggesting that on-time injections are even more important with less frequent dosing.

The SOLAR study found that Cabenuva taken every two months maintained viral suppression for people who switched from the daily Biktarvy combination pill (bictegravir/tenofovir alafenamide/emtricitabine). Finally, the FLAIR trial found that Cabenuva is also highly effective for first-line treatment. Across the studies, the most common side effect was mostly mild to moderate injection site reactions, which participants found acceptable.

“It’s going to be a trade-off between the burden of daily oral therapy versus the freedom of two-monthly treatment with the potential for resistance in a very small number of people. It’s important that people have the chance to make their own decisions,” says Orkin, who led the FLAIR study.

Susan Swindells (left) and Chloe Orkin present results from the ATLAS and FLAIR trials.Liz Highleyman

So far, Cabenuva is approved only for adults and adolescents who already have an undetectable viral load and wish to switch to a more convenient regimen. But it may also be a feasible approach for people starting treatment for the first time and those who have been unable to achieve or maintain viral suppression due to challenges with adherence.

Monica Gandhi, MD, MPH, and her team at San Francisco General Hospital’s Ward 86 HIV clinic evaluated outcomes among 133 people who switched to Cabenuva from a daily oral regimen. Two thirds were homeless or lacked stable housing, and many were dealing with substance use and mental health problems. They received intensive support, including case management, phone or

text reminders of upcoming injection visits, follow-up for missed appointments and even street-based nursing services.

A majority of the study participants already had an undetectable viral load on their current medications, and all of them maintained viral suppression after switching to the injections. The more exciting finding was that outcomes were nearly as good for the 57 people who started with a detectable viral load: All but two achieved viral suppression.

“For those of us treating HIV on a daily basis, we know that some patients have challenges taking pills, including substance use, housing and food insecurity and stigma,” Gandhi told POZ. “By trying to use these novel agents in patients with concomitant life challenges, we hope to get individuals suppressed on therapy who have never been suppressed before and change the trajectory of the HIV epidemic.”

For HIV prevention, ViiV’s Apretude (injectable cabotegravir alone), approved by the FDA in December 2021, is currently the sole long-acting PrEP option. According to the Centers for Disease Control and Prevention, only about 25% of the more than 1 million people who could benefit from PrEP have received a prescription for it. A prevention method that doesn’t have to be taken daily could potentially increase uptake and adherence.

Two large trials showed that Apretude administered every other month works even better than daily tenofovir disoproxil fumarate/emtricitabine PrEP pills (Truvada and generic equivalents). HPTN 083, which enrolled more than 4,500 cisgender men and transgender women who have sex with men, showed that the injections were 69% more effective at preventing HIV acquisition—a remarkable finding, given that daily oral PrEP reduces the risk of HIV acquisition by about 99% for gay and bisexual men who use it consistently. HPTN 084, which compared Apretude versus daily PrEP pills for more than 3,000 mostly young cisgender women in Africa, found that the injections were about 90% more effective.

Cabenuva and Apretude currently must be administered by a health care provider, but this could change. Recent studies found that high-concentration formulations of injectable cabotegravir and rilpivirine could allow for lower-volume shots and that alternative injection sites—such as the thigh or belly—are feasible. This suggests that people could potentially administer long-acting treatment or PrEP themselves, meaning fewer clinic visits and less need for health care staff and resources.

What’s in the Pipeline?

Injectable antiretrovirals taken less often than every other month, as well as longer-acting oral therapies, could further increase convenience and improve adherence to HIV treatment and PrEP.

Gilead Sciences’ Sunlenca (lenacapavir), the first HIV capsid inhibitor, was approved last December but only for treatment-experienced adults with multidrug-resistant virus who are unable to maintain viral suppression on their current regimen. Trogarzo (ibalizumab), an injection every two weeks, is also approved for heavily treatment-experienced adults. Both are good news for

long-term survivors who used suboptimal drugs early in the epidemic and developed resistance that leaves them with few treatment options.

Long-acting therapy won’t matter, and it won’t work, if people don’t know about it, have confidence in it or have access to it.

Sunlenca is available as an injection given once every six months and as a pill that is currently used only as a loading dose prior to injections. In the CAPELLA trial, twice-yearly Sunlenca injections plus an optimized background regimen led to viral suppression in more than 80% of treatment-experienced people with highly resistant HIV. The participants had been living with HIV for 24 years, on average, and they had previously tried a median of 11 antiretrovirals. The response rate was lower (67%) for people with no other fully active drugs in their background regimens, but still quite impressive given such highly resistant virus. CD4 T-cell counts rose, and the proportion of people who met the criteria for AIDS (less than 200 CD4 T cells) fell from 75% to 40%.

Sunlenca also works well for people new to treatment, but it is not yet approved for this indication. The CALIBRATE trial showed that 85% to 90% of participants who received Sunlenca injections every six months along with a single daily oral antiretroviral (tenofovir alafenamide or bictegravir) had an undetectable viral load after a year of treatment. In both studies, Sunlenca was safe and generally well tolerated; here, too, the most common side effect was mild to moderate injection site reactions.

As it stands, Sunlenca must be taken with daily pills for HIV treatment, thereby limiting its promise as a twice-yearly option. Targeting two or more steps of the viral life cycle is necessary to keep HIV in check over the long term, but so far, Sunlenca has no equally long-acting partners to make up a complete semiannual regimen.

On the other hand, solo Sunlenca shows promise as a twice-yearly option for PrEP. While combination therapy is needed to fully control HIV, a single drug can be enough to prevent the virus from taking hold in the body.

Oral agents with extended anti-HIV activity are also in the pipeline. Merck’s islatravir, the first nucleoside reverse transcriptase translocation inhibitor, stays in the body long enough to allow for once-weekly dosing. Islatravir also shows potential for HIV prevention. Unfortunately, the FDA put clinical trials of islatravir on hold in December 2021 after HIV-positive participants in treatment trials experienced declining CD4 counts and HIV-negative volunteers in PrEP studies saw a drop in their total lymphocyte counts.

But Merck was not ready to give up on islatravir. Company scientists conducted an extensive analysis to better understand the problem, determining that the doses used in these trials were probably too high. People who took a lower dose had CD4 and total lymphocyte changes comparable to those seen in people on standard daily therapy. Merck thus resumed Phase III studies testing a 0.25 milligram dose of islatravir in a daily regimen with Pifeltro (doravirine), while Merck and Gilead restarted a Phase II trial assessing a once-weekly combination of 2 mg islatravir plus Sunlenca pills.

The future of islatravir for HIV prevention is murkier. Company-sponsored studies of once-monthly islatravir for PrEP have been discontinued due to side effects, but independent researchers are continuing to evaluate long-lasting islatravir implants that could potentially offer protection for years, like long-acting contraceptives.

As reported at this year's Conference on Retroviruses and Opportunistic Infections, one research team tested a refillable islatravir implant 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. A cabotegravir implant that could offer longer-lasting protection than Apretude injections is also in the works.

Further back in the pipeline, broadly neutralizing antibodies, a type of immunotherapy, hold promise for both treatment and prevention (see sidebar below).

Ultimately, the longest HIV treatment would be a cure, and the longest PrEP would be a vaccine. Antiretroviral therapy still has side effects, and chronic HIV infection can lead to health problems even for people with an undetectable viral load. What's more, providing lifelong treatment or PrEP for millions of people worldwide is a daunting challenge.

Dázon Dixon DialloCourtesy of Dázon Dixon Diallo

But cure research is proceeding slowly, and the field has seen many disappointments. HIV vaccine research, too, has seen numerous failures, most recently the premature discontinuation of the large Mosaico trial after interim results showed that an experimental adenovirus vector HIV vaccine did not provide protection.

While researchers aren't giving up on a cure or a vaccine, people living with or at risk for HIV can in the near term look forward to treatment and prevention options that can be taken less often, potentially making it easier to stay on therapy, keep the virus under control and achieve a better quality of life. But this promise must be available to everyone who could benefit.

"The fight to end HIV cannot be won with a 'one-size fits all' approach," says Dázon Dixon Diallo, MPH, president of the women's HIV and AIDS nonprofit SisterLove in Atlanta. "Like daily oral therapy, [long-acting therapy] won't matter, and it won't work, if people don't know about it, have confidence in it or have access to it. Accessibility, acceptability and affordability all matter for those who need it most, especially people of African descent worldwide."

Broadly Neutralizing Antibodies

Most people living with HIV make antibodies against the virus, but HIV mutates rapidly and is usually able to escape them. However, a small proportion of people produce broadly neutralizing antibodies (bnAbs) that target parts of the virus that don't change very much. Engineered versions of these antibodies are now being studied for prevention, treatment and a functional cure.

The Antibody-Mediated Prevention (AMP) trial showed that a bnAb dubbed VRC01 had little effect on most strains of HIV, but it did lower the risk of acquiring virus strains that were sensitive to the antibody by 75%. Experts predict that they might have more success using cocktails of bnAbs to overcome resistance. Scientists are also working on experimental mRNA vaccines designed to train immature B cells to produce bnAbs in the body.

For treatment, researchers at Rockefeller University tested a combination of two bnAbs (10-074 and 3BNC117) given at two- to three-week intervals over five months in people with chronic HIV. They found that the antibodies delayed viral rebound after stopping antiretroviral therapy: 13 out of 17 participants who discontinued antiretrovirals two days after the first bnAb infusions maintained viral suppression for at least five months, and two people did so for a year.

This approach might work better for people who start antiretroviral treatment at an early stage of HIV infection. In one study, 14 people received up to eight monthly infusions of 10-074 and 3BNC117 or a placebo. None of the seven participants who received the bnAbs had to restart antiretrovirals before seven months post-infusion, while six of the seven who received the placebo did so. But again, this didn't work for people whose virus was resistant to one or both of the antibodies. Other researchers found that more than 40% of children born with HIV who switched from oral antiretrovirals to infusions

of two bnAbs (VRC01LS and 10-1074) administered every four weeks maintained an undetectable viral load for six months.

Long-acting antibodies are also being tested as a potential partner for Sunlenca. In a small Phase I trial, 21 people with an undetectable viral load stopped oral antiretrovirals and received Sunlenca injections plus infusions of two bnAbs, teropavimab (a long-acting form of 3BNC117) and zinlirvimab (derived from 10-074). Participants were tested in advance to ensure that their HIV was susceptible to both antibodies. Six months later, 90% still had viral suppression. Next, a Phase II trial will assess whether viral suppression can be maintained when the regimen is administered semiannually for a longer duration.

“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,” says lead investigator Joseph Eron, MD, of the University of North Carolina at Chapel Hill.
