The Long & Winding Road

After advances in HIV therapy, long-acting antiretrovirals and long-term remission are the next frontiers.

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HIV care has come a long way in the more than 40 years since the Centers for Disease Control and Prevention published the first report of AIDS in June 1981. The combined efforts of researchers, clinicians, public health officials, activists and people living with HIV have led to amazing advances in prevention and treatment. And despite many setbacks, cure research is also making progress.

The earliest antiretroviral drugs, such as AZT, were only marginally effective. Although they could halt HIV replication temporarily, the virus soon developed resistance. The first big breakthrough came in the mid-1990s with the advent of highly active antiretroviral therapy, drug cocktails that include HIV protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTIs). By targeting multiple steps of the viral life cycle, combination therapy was able to keep HIV in check over the long term.

The new regimens were unbelievably effective, knocking viral load down to an undetectable level and allowing CD4 T-cell counts to recover enough to prevent opportunistic illnesses. Within a year after their introduction, AIDS-related hospitalization and death began a steep decline. But the early cocktails were difficult to use, sometimes involving handfuls of pills taken multiple times a day with strict food requirements. What's more, early antiretrovirals often came with drug interactions and side effects that made it hard to maintain adherence.

But scientists never let up on their efforts to develop better treatment, and activists, while demanding access for all, never stopped pushing for meds that were more effective, better tolerated and easier to take.

In 2006, the Food and Drug Administration (FDA) approved Atripla, the first once-daily single-tablet regimen, or all-in-one pill. The following year, the first integrase inhibitor made its debut. And in 2021, the FDA approved Cabenuva (cabotegravir/rilpivirine), the first complete long-acting injectable regimen.

In parallel, researchers have made remarkable advances in biomedical prevention. In 2012, the FDA approved Truvada for pre-exposure prophylaxis (PrEP), a once-daily pill that lowers the risk of HIV acquisition by around 99%. Earlier this year, the agency gave the nod to Apretude (cabotegravir), a long-acting PrEP injection administered every other month. And despite many

failures, scientists and advocates have not lost sight of their original goal of an effective HIV vaccine.

Today, most people living with HIV can control the virus with a single once-daily pill or every-other-month injections, and those who start treatment promptly and receive good care can expect a near-normal life span. But researchers and advocates are working on further improvements to fill the remaining gaps. These include more effective meds for long-term survivors with extensive drug resistance and simpler, more affordable regimens for people who still struggle with access and adherence.

Even with improvements in prevention and treatment, a cure remains the holy grail of HIV research. A small number of people have provided proof of concept that a cure—or at least long-term remission, sometimes called a functional cure—is possible. Today, scientists are exploring a wide range of strategies to achieve a broadly accessible functional cure for the nearly 40 million people living with HIV worldwide.

Long-Acting Treatment

Although daily antiretroviral therapy is highly effective, it requires thinking about HIV and remembering to take pills 365 days a year, so long-acting treatment has been eagerly awaited.

The first complete long-acting regimen, Cabenuva, was initially approved as a once-monthly injection, but in February, the FDA approved an every-other-month regimen.

Cabenuva consists of an extended-release formulation of ViiV Healthcare's integrase inhibitor cabotegravir plus an injectable version of Janssen's NNRTI rilpivirine. It involves two intramuscular injections in the buttocks administered by a health care provider.

The ATLAS trial showed that people who switched from a standard oral regimen to monthly Cabenuva were about as likely to maintain viral suppression as those who stayed on daily pills. The ATLAS-2M study showed that those who received the injections every eight weeks responded as well as those who did so every four weeks. The FLAIR trial found that Cabenuva is also effective for first-line treatment. For HIV prevention, studies showed that Apretude—cabotegravir injections alone—work even better than daily PrEP pills, which are highly effective.

Study participants reported greater satisfaction with Cabenuva or Apretude compared with daily oral treatment or PrEP. Reasons for preferring the injections include greater convenience—which can lead to better adherence—and not having pill bottles that could reveal one's HIV status or risk.

Chloe Orkin, MDLiz Highleyman

But access to Cabenuva remains a challenge. “Although these therapies may be my present tense, they still represent the future for many people worldwide,” says Chloe Orkin, MD, of Queen Mary

University of London, who gave an overview of the future of HIV treatment and prevention at this year's Conference on Retroviruses and Opportunistic Infections (CROI). "It's really important that new compounds are accessible everywhere and that they are not the domain of the rich."

Speaking at a CROI community forum, Jim Pickett, a senior adviser at AVAC, noted that while the recent approval of an every-other-month regimen is a big deal—some people will now be able to take their HIV treatment just six times a year—new formulations that could be self-administered would be even better. "You can imagine people being able to give shots themselves or have someone else give them a shot at home. What a revolution that would be!"

Two other long-acting meds, Merck's islatravir and Gilead Sciences' lenacapavir, have shown promise in clinical trials. Islatravir, the first nucleoside reverse transcriptase translocation inhibitor, showed good activity in a once-daily combination with the NNRTI doravirine, but because doravirine is not suitable for long-acting therapy, Merck paired islatravir with its experimental long-acting NNRTI, MK-8507, in a once-weekly regimen. Islatravir is also being studied for PrEP, both as a once-monthly oral regimen and as an implant that could potentially provide protection for a year.

Lenacapavir, a long-acting HIV capsid inhibitor, works differently than existing drugs and remains active against virus that has developed resistance to other antiretroviral classes. This is good news for people with long-term HIV who used suboptimal drugs—sometimes one at a time—early in the epidemic and have multidrug resistance that leaves them with few treatment options.

As reported at CROI, the CAPELLA trial showed that twice-yearly lenacapavir injections plus an optimized background regimen led to viral suppression in more than 80% of heavily treatment-experienced people with multidrug-resistant HIV. Likewise, the CALIBRATE trial showed that lenacapavir injections plus a single oral antiretroviral suppressed the virus in people starting treatment for the first time. Lenacapavir is also being studied as a twice-yearly PrEP option.

But both drugs have hit snags in their development. Trials of islatravir were put on hold late last year after HIV-positive participants in treatment trials experienced declining CD4 counts and HIV-negative volunteers in PrEP studies saw a drop in total lymphocyte counts. The future of islatravir is currently unclear. Studies of lenacapavir were also paused last December due to concerns about the type of glass vial used for the injectable formulation, but the FDA lifted the hold in May, after Gilead switched to a different type of glass.

Further back in the pipeline, broadly neutralizing antibodies (bnAbs), a type of immunotherapy, hold promise for treatment, prevention and cure strategies. Other novel candidates include two HIV maturation inhibitors from GSK.

Most people with HIV do make antibodies against the virus, but HIV mutates rapidly and is usually able to escape them. However, some people can produce more broadly active antibodies that target parts of the virus that don't change much. Engineered versions of these antibodies are now under study.

Research presented at CROI showed that more than 40% of children born with HIV who switched from oral antiretrovirals to monthly infusions of two bnAbs (VRC01 and 10-1074) maintained an undetectable viral load for six months. The Antibody Mediated Prevention trials, which tested bnAbs for PrEP, found that VRC01 did not prevent HIV overall, but it did lower the risk of acquiring HIV strains that were sensitive to the antibody. Experts expect that bnAb cocktails will be needed to overcome viral resistance.

“Long-acting therapies are a paradigm shift in how we deliver care,” according to Orkin. But she acknowledges that drug resistance may be a cost of long-acting treatment. “It’s going to be a trade-off between the burden of daily oral therapy versus the freedom of six-monthly treatment with the potential for resistance in a very small number of people,” she says. “It’s important that people have the chance to make their own decisions.”

Cure Research

Despite advances in HIV treatment, many people living with the virus hold out hope for a cure. Some people still experience side effects from antiretroviral therapy, and chronic HIV infection can lead to a host of health problems even in people with an undetectable viral load. What’s more, providing lifelong treatment for the millions of people with HIV worldwide is a daunting challenge.

Steven Deeks, MDJan Brittenson

“I’m not sure complete HIV eradication is going to be achievable, but near-complete eradication

with a little help from the immune system is where we believe the action is," cure researcher Steven Deeks, MD, of the University of California San Francisco told POZ (see "Searching for a Cure."). "I'm more optimistic than ever that in 10 years we will be studying something that could very well work."

Scientists are exploring many avenues in the search for a cure. While antiretrovirals can keep HIV replication under control as long as treatment continues, the virus inserts its genetic blueprint into the chromosomes of human cells and establishes a long-lasting latent reservoir that is unreachable by antiretrovirals and usually invisible to the immune system. These so-called HIV proviruses can lie dormant in resting immune cells indefinitely in the presence of antiretrovirals, but they usually start churning out new virus soon after the drugs are discontinued.

"Over the past decade, HIV cure research has greatly intensified, but it remains clear that we will not cure HIV until we better understand where and how the virus hides and we also get much better at measuring the HIV reservoir," says Sharon Lewin, MD, director of the Peter Doherty Institute for Infection and Immunity in Australia.

The past decade has seen some progress in the quest for a functional cure, but there have also been several disappointments. Only a few people are widely regarded as cured: the late Timothy Ray Brown (the Berlin Patient), Adam Castillejo (the London Patient) and possibly an anonymous woman dubbed the New York Patient. All of them received stem cell transplants from donors with a rare genetic mutation (CCR5-delta32) that blocks HIV from entering cells. But this procedure is far too risky for people who don't need it to treat life-threatening cancer.

Researchers have identified a small number of people who manage to naturally control HIV. Some (known as elite controllers) have never taken antiretroviral therapy, while others (known as posttreatment controllers) have been able to maintain viral suppression after stopping antiretrovirals. Two women, Loreen Willenberg (the San Francisco Patient) and the anonymous Esperanza Patient in Argentina, appear to have eliminated HIV without ever taking antiretrovirals, and they may have achieved a natural cure.

While such individuals are exceptional, they offer proof of concept that a functional cure is possible and offer clues that could help scientists achieve long-term remission for more typical people living with HIV.

Researchers are exploring a wide range of cure strategies including "kick and kill," which tries to flush dormant virus out of hiding using latency-reversing agents, and "block and lock," which aims to keep latent proviruses in a permanent sleep. Some approaches attempt to replicate Brown's cure by cutting out or turning off the CCR5 receptors HIV uses to enter cells. Another strategy uses CRISPR technology to snip HIV proviruses out of chromosomes. Still other approaches help the immune system fight HIV.

Experimental interventions include drugs, therapeutic vaccines, broadly neutralizing antibodies, engineered T cells and gene therapy. One promising approach involves inserting genes into long-lived cells that could make antibodies forever. Vaccine technology—including mRNA—has

improved during the COVID-19 era, and experimental therapeutic vaccines have already cured monkeys.

Most experts think combination approaches will work best. Deeks is currently leading a study—among the most complex cure trials to date—that combines a therapeutic vaccine, bnAbs and a TLR9 agonist to flush HIV out of hiding and control residual virus (see "My HIV Cure Trial.").

Cure studies often require participants to undergo multiple procedures over an extended period. Ultimately, they are asked to temporarily stop treatment, with careful monitoring, to see whether they can maintain viral suppression without antiretrovirals. The studies now underway are not expected to cure the participants, but they will advance the science and help other people with HIV in the future.

"Our studies are very intensive, and they have a fair amount of risk. Everyone is aware that these early studies aren't going to cure anyone," Deeks says. "The main reason people join these studies is altruism, and I haven't seen altruism in the community so strong since the '90s."

While these approaches may today seem like science fiction, researchers and advocates won't be satisfied with just a few exceptional success stories. When it comes to long-acting treatment and a functional cure, they want widely accessible and affordable options for all people living with HIV. It took years after the advent of effective antiretroviral therapy for the medications to reach people in low-income countries. That's a history no one wants to repeat.

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