HIV at 45: The Evolution of HIV Prevention, Treatment and Cure

Advances in lifesaving antiretroviral treatment and PrEP have been remarkable, but further progress depends on continued funding for HIV research.

June 5, 2026 By Liz Highleyman

The first medical report of AIDS was published in the Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report 45 years ago today, on June 5, 1981. The first antiretroviral drug, AZT, was approved in 1987, but it took nearly a decade longer to develop effective combination therapy that kept the virus in check and another 16 years until the approval of daily pills to prevent HIV.

The evolution of HIV prevention and treatment is among the most remarkable 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. But while HIV treatment and pre-exposure prophylaxis (PrEP) have steadily improved, an HIV vaccine and a functional cure remain elusive.

"Without question, current treatment and PrEP options work great. They are effective and safe, and they are getting better and better every year," Steven Deeks, MD, of the University of California San Francisco told POZ. "But they require an individual to remain engaged in the healthcare system for life and to adhere to lifelong therapy. This is just not feasible for many. To end the epidemic, we will need a one-and-done approach for treatment or prevention. In other words, we will likely need a scalable cure or a vaccine, preferably both."

HIV Treatment

Modern HIV treatment is highly effective, generally well tolerated and most people can take a single-tablet regimen that combines two or three drugs in one daily pill. The newest, Merck's Idvynso (doravirine/islatravir), was approved in April. Researchers are now testing islatravir in combination with Merck's NNRTI ulonivirine and with Gilead Sciences' HIV capsid inhibitor lenacapavir as potential once-weekly oral options.

But some people have difficulty maintaining good adherence to daily oral treatment because they sometimes forget to take their pills, don't want to think about having HIV every day or are living in situations where their medications could be lost or stolen. This will likely still be the case with weekly pills, so longer-acting injectables are the wave of the future.

Today, the longest-acting complete regimen is ViiV Healthcare's Cabenuva (injectable cabotegravir and rilpivirine), which is administered once monthly or every other month. An injectable formulation of lenacapavir (branded as Sunlenca) is given just twice a year, but it currently has no equally durable partners to build a complete treatment regimen.

That's likely to change in the coming years. At this year's Conference on Retroviruses and Opportunistic Infections, researchers reported promising early data on experimental antiretrovirals from ViiV (VH184 and VH499) and Gilead (GS-3242) that could potentially be given every six months. Both companies are also working on broadly neutralizing antibodies, which target hidden parts of the virus, as partners for long-acting injectable antiretrovirals.

HIV Prevention

Turning to prevention, the daily PrEP pills Truvada (tenofovir disoproxil fumarate/emtricitabine) and Descovy (tenofovir alafenamide/emtricitabine) reduce the risk of HIV acquisition by around 99% if used consistently. Yet only about a third of the estimated 1.2 million people who could benefit from PrEP are using it, according to the CDC. Clinicians and advocates hope longer-acting options can help close the gap.

Last year's big news was the approval of injectable lenacapavir (branded as Yeztugo) for twice-yearly PrEP. In two large studies, lenacapavir PrEP dramatically reduced HIV acquisition among young cisgender women in Africa and gay and bisexual men and gender-diverse people in the United States and six other countries. Early studies suggest that the interval could potentially be extended to once yearly. But lenacapavir's high price and lack of clarity about insurance coverage have slowed its rollout in the United States, and federal funding cuts have limited its distribution in low-income countries.

"We've made tremendous strides in both HIV prevention and treatment over the last few decades. Now, a person who may be exposed to HIV can prevent infection with a single shot every two months, a double shot every six months, daily pills or pills just around the time of sex," said Susan Buchbinder, MD, director of Bridge HIV at the San Francisco Department of Public Health. "There are new products in development—shots maybe as infrequently as once a year and a monthly pill, both of which could be further major breakthroughs in HIV prevention. However, we still need HIV prevention and treatment research to make regimens easier to take, to address individual's needs

for products, to study how to scale up prevention and treatment and hopefully to get us to an effective HIV vaccine and HIV cure."

A twice-yearly shot may seem vaccine-like, but lenacapavir is an antiretroviral drug that stops HIV replication, not a vaccine that trains the immune system to fight the virus. Like Deeks, many experts think that only a vaccine—in particular, one that offers durable protection—can end the epidemic.

Despite decades of effort and billions of dollars, HIV vaccine research has yielded a string of disappointments. One after another, traditional vaccine approaches have failed to provide protection in clinical trials. The last large trial, PrEPVacc, was halted in 2023 after data showed that there was little or no chance that the tested vaccines would demonstrate efficacy.

But scientists have not given up, turning to more sophisticated strategies. Some studies have tested broadly neutralizing antibodies for prevention, but again, results have been disappointing. Currently, the most promising avenue is germline targeting, which uses a series of primer and booster vaccines to train the immune system to produce its own broadly neutralizing antibodies. If this approach requires multiple vaccines given over time, however, it might be no more practical than long-acting PrEP.

"A vaccine generally mimics the body's natural immune reaction to a virus, which usually results in it being cleared," former National Institute of Allergy and Infectious Diseases director Anthony Fauci, MD, once explained. "But with HIV, it doesn't. So a vaccine has to elicit an immune response that's better than nature, and that's hard to do."

Cure Research

The ultimate goal of the HIV field is a cure, but here too, research has proceeded slowly with many setbacks. While antiretrovirals can suppress viral replication indefinitely, HIV inserts its genetic blueprints into the DNA of human cells and establishes a long-lasting viral reservoir that is unreachable by antiretrovirals and usually invisible to the immune system, making a true cure nearly impossible. Even with treatment, HIV causes persistent immune activation and chronic inflammation that can lead to a host of health problems and accelerated aging.

Only 11 people are known to have been cured after stem cell transplants for cancer treatment, most recently the Toronto Patient, whose case was presented at the Canadian Association of HIV Research Conference in April. The procedure is too risky for people without life-threatening cancer, but each new case offers clues that could help scientists develop a more accessible functional cure, or long-term remission without antiretrovirals.

Many functional cure approaches have been studied, such as locking HIV in an inactive state so it can never replicate, flushing the virus out of resting cells so it becomes susceptible to antiretrovirals, and boosting the immune system to better recognize and attack the virus.

Deeks recently presented findings from a small study of CAR-T therapy for HIV at the American

Society of Cell and Gene Therapy annual meeting last month. Best known as a treatment for cancer, CAR-T involves removing a sample of a patient's T cells, inserting artificial receptors and reinfusing the "living drug" back into the body.

Of the nine participants who received T cells reprogrammed to target HIV, one has maintained an undetectable or very low viral load for nearly two years after stopping antiretroviral treatment, a second has been in remission for almost a year and a third showed transient viral control for about three months. All three started antiretrovirals soon after infection, adding to the evidence that very early treatment improves the prospects for a functional cure.

Many experts think that achieving a functional cure will require a combination approach. Current strategies are complex and expensive, however, so they are unlikely to be accessible to the millions of people living with HIV worldwide, largely in resource-limited countries. On the other hand, this is just the population that stands to benefit most from a one-and-done cure because they have limited or sporadic access to lifelong antiretroviral treatment, especially given cuts to international aid.

While an HIV vaccine and a functional cure remain on the distant horizon, people living with HIV can look forward to better prevention and treatment options in the near and medium-term future. But continued progress requires steady funding of medical research, which is jeopardized under the Trump administration.

"As the HIV community reflects on the first report of HIV/AIDS in the U.S. by the CDC 45 years ago and honors the lives lost and those saved by the availability of HIV prevention and treatment, the House of Representatives once again advanced a bill that would upend decades of progress in fighting HIV," HIV Medicine Association chair Anna Person, MD, said in a statement.

"The bill passed by the House Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies would eliminate CDC's core HIV prevention program and parts of the Ryan White HIV/AIDS Program at a time when the demand for HIV services is at an all-time high and millions of people risk losing their Medicaid coverage," she added. "We call on Congress to reject these proposals and fund federal HIV programs at the levels necessary to end the HIV epidemic once and for all."

An earlier version of this article was published in the Bay Area Reporter on June 1, 2026.

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