HIV Treatment: 40 Years of Innovation

Treatment for the virus has come a long way since the first antiretroviral approval 1987, but more advances are yet still ahead.

May 17, 2021 By Liz Highleyman

Many long-term HIV survivors can remember the early days of antiretroviral therapy all too well: handfuls of pills taken multiple times a day, complex food requirements, difficult side effects and the ever-present threat of drug resistance. What's more, the meds often couldn't keep the virus fully under control.

But things have come a long way in the past 34 years, from the advent of effective combination therapy in the mid-1990s to the first once-daily single-tablet regimen to the approval of pre-exposure prophylaxis to the first complete long-acting injectable regimen in 2021.

The development of effective HIV treatment, which has turned an inexorably fatal disease into a chronic, manageable illness, is among the most impressive medical breakthroughs of our lifetime. But challenges still remain, and researchers are hard at work on new advances that could enable people living with HIV to take medications less often or even achieve a functional cure.

A History of Breakthroughs

The first medical report of the disease that would come to be known as AIDS appeared in the June 5, 1981, edition of Morbidity and Mortality Weekly Report (MMWR), a weekly epidemiology digest from the Centers for Disease Control and Prevention (CDC). Doctors described five unusual cases of Pneumocystis pneumonia (PCP) among young gay men in Los Angeles. A month later, MMWR published a second report on cases of PCP and Kaposi sarcoma in New York City and California, and the July 3 New York Times ran an article titled "Rare Cancer Seen in 41 Homosexuals."

Before long, it became clear that these and other similar cases resulted from a breakdown of the immune system, rendering it unable to fight off infections or protect against opportunistic cancers. The mysterious syndrome was also seen in people with hemophilia, people who inject drugs and newborn infants, suggesting it was caused by an infectious pathogen transmitted in blood.

In 1983 and 1984, French and American scientists independently announced the discovery of the retrovirus that causes AIDS, which they eventually agreed to name human immunodeficiency virus, or HIV. The discovery of the virus set in motion a globaleffort to find treatments, vaccines and—hopefully—a cure.

In the early years of the epidemic, people living with HIV tried countless therapies, ranging from vitamin C to ribavirin to compound Q, with minimal success. In March 1987, the Food and Drug Administration (FDA) approved the first antiretroviral, AZT (Retrovir, or zidovudine). Although the drug blocked HIV replication in the short term, it cause severe side effects. What's more, it soon became apparent that the virus was able to develop resistance to a single drug, and combination therapy would likely be necessary.

Over the next few years, researchers—spurred on by AIDS activists—developed other nucleoside reverse transcriptase inhibitors (NRTIs), including ddI (Videx), ddC (Hivid), and d4T (Zerit). But because they were in the same drug class as AZT, they targeted HIV in a similar way, and, even when combined, they couldn't control the virus for long.

The big breakthrough came in the mid-1990s with the approval of the first protease inhibitors, Invirase (saquinavir) in December 1995 and Crixivan (indinavir) in March 1996. Later that year, the first non-nucleoside reverse transcriptase inhibitor (NNRTI), Viramune (nevirapine), was added to the armamentarium.

Combining drugs that target different steps of HIV's lifecycle finally provided the punch needed to keep the virus under control. The 1996 International AIDS Conference in Vancouver had an air of celebration as researchers reported on the benefits of the new drug cocktails. Within a year, AIDS deaths had dropped by nearly half.

But taking the cocktails was an ordeal, requiring multiple pills up to three times a day. Many people with HIV also needed other medications to prevent or treat opportunistic illnesses, adding to their pill burden. And before long, unexpected side effects began to appear, including worrisome metabolic abnormalities and body shape changes known as lipodystrophy.

Improving Treatment and Prevention

But researchers didn't stop there, continuing their quest to develop more convenient, better tolerated and more effective antiretrovirals.

The first nucleotide reverse transcriptase inhibitor, tenofovir disoproxil fumarate (TDF), was approved in 2001, paving the way in 2006 for the first single-tablet regimen, Atripla (efavirenz/TDF/emtricitabine), which required just one pill once daily. The following year saw the debut of Isentress (raltegravir), the first of the potent and well-tolerated new class of integrase inhibitors.

Along with new medications, researchers and clinicians also learned more about how best to use antiretroviral treatment. The advent of better drugs raised the question of whether prompt, potent treatment—dubbed "hit early, hit hard"—could potentially eliminate HIV, but that hope proved elusive.

In an effort to limit drug side effects while preserving immune function, treatment guidelines from the Department of Health and Human Services (DHHS) raised and lowered the CD4 cell threshold

for starting treatment according to the latest research. The first edition, in 1998, recommended starting when CD4s fell below 500; later versions set the threshold at 350 and even 200 (an AIDS diagnosis). Some researchers and advocates thought periodic treatment interruptions might help reduce drug toxicities, but in 2006, the SMART study confirmed that treatment breaks are risky.

It turned out that some of the problems blamed on the drugs were more likely attributable to chronic HIV infection and persistent inflammation, which contributes to the many health conditions that occur more often and at an earlier age in people with HIV. But this can be minimized if people start treatment promptly and keep their viral load suppressed. In fact, people who start treatment soon after diagnosis have a life expectancy similar to that of the general population.

In 2010, San Francisco was the first city to recommend that everyone diagnosed with HIV should start antiretroviral therapy as soon as possible, regardless of CD4 count; the DHHS followed suit two years later. In 2015, the START trial confirmed that starting treatment early results in better outcomes than waiting until a person's CD4 count falls below 350, leading the World Health Organization to embrace universal treatment.

HIV treatment has not been the only realm of innovation. As early as 1994, researchers learned that giving AZT to pregnant women during gestation and delivery as well as to their newborns could prevent mother-to-child transmission. Antiretrovirals, if taken within 72 hours, can also prevent HIV from taking hold after an accidental exposure, an approach known as post-exposure prophylaxis, or PEP.

Building on these findings, researchers began to study whether antiretrovirals could be taken in advance to prevent sexual transmission of HIV. Results from the iPrEx trial, reported in 2010, showed that Truvada (TDF/emtricitabine) could reduce the risk of sexual transmission of HIV among men who have sex with men by more than 90%. The FDA approved Truvada for PrEP in 2012. The French Ipergay study later showed that taking PrEP "on demand" before and after sex is also highly effective for gay and bisexual men.

In 2011, researchers presented the first definitive evidence, from the HPTN 052 trial, that people on effective antiretroviral therapy with a sustained undetectable viral load do not transmit HIV to their sexual partners. Thus was born the idea of treatment as prevention, or Undetectable Equals Untransmittable (U=U).

Innovation Continues

While modern antiretroviral therapy is highly effective and can usually control HIV, some people—in particular, long-term survivors with extensive treatment experience and highly resistant virus—can have trouble reaching or maintaining an undetectable viral load. For them, Rukobia (fostemsavir), the first HIV attachment inhibitor, or Trogarzo (ibalizumab), the first monoclonal antibody therapy for HIV, may be a lifesaver.

People who start treatment early have more options. The potent integrase inhibitor Tivicay (dolutegravir), approved in 2013, can keep HIV suppressed with just one other drug, instead of the

previous standard three-drug regimens.

For those who wish to take medications less often, Cabenuva (cabotegravir/rilpivirine), the first complete long-acting injectable regimen, may be an option. Approved in January 2021, Cabenuva is administered by a health care provider once a month. Studies show that administration every other month is equally effective, offering the prospect of receiving treatment just six times a year (an every-other-month schedule is under consideration by the FDA). Cabotegravir alone every other month is also highly effective for HIV prevention.

Other long-acting medications are in the pipeline. Islatravir, the first nucleoside reverse transcriptase translocation inhibitor, has a long half-life in the body and is being studied as part of a once-weekly oral regimen in combination with Merck's experimental long-acting NNRTI MK-8507. Oral islatravir also has the potential to be used once monthly for HIV prevention, and an islatravir PrEP implant could provide protection for a full year.

Recent research shows that lenacapavir, the first HIV capsid inhibitor, suppresses viral load in highly treatment-experienced people with multidrug-resistant virus. Lenacapavir for HIV treatment is expected to work for at least six months, and it is also being studied as a long-acting PrEP option.

Ultimately, the holy grail of HIV treatment is a functional cure, meaning people can maintain viral suppression without antiretrovirals for a prolonged period. Currently, a functional cure remains elusive, but numerous therapies are under study, including broadly neutralizing antibodies and therapeutic vaccines, which have the potential to be used together as part of a combination approach. Likewise, the quest for a preventive vaccine has yet to bear fruit, but this remains an active area of research.

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