New Year, New Treatment?

HIV treatment has come a long way, but there's still room for innovation.

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The start of a new year is a good time to take stock of your HIV treatment and ask whether it's still the best option for you. Many people living with HIV—especially those who started treatment recently—are on effective, well tolerated regimens, but you still might be able to take advantage of new innovations in antiretroviral therapy.

The development of effective HIV treatment, which has turned an inevitably fatal disease into a chronic, manageable condition, is among the most impressive medical breakthroughs in history. Since the first antiretroviral was approved in 1987, activists have not stopped pushing for new and better options, and researchers have not let up on their quest to make treatment more effective, better tolerated and easier to use.

Three Decades of Innovation

The first medical report of the disease that would come to be known as AIDS appeared in the June 5, 1981, edition of the Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report. This and subsequent reports described unusual cases of pneumonia and a rare cancer in young gay men in California and New York.

Before long, it became clear that these cases resulted from a breakdown of the immune system, leaving people unable to fight off opportunistic infections and cancers. Two years later, French scientists reported the discovery of the retrovirus that causes AIDS, which was eventually named human immunodeficiency virus, or HIV. This discovery spurred a global effort to find vaccines, treatments and a cure for the deadly disease.

In March 1987, the Food and Drug Administration (FDA) approved the first antiretroviral, Retrovir (AZT, or zidovudine), followed by three more nucleoside reverse transcriptase inhibitors—Videx (ddI, didanosine), Hivid (ddC, or zalcitabine) and Zerit (d4T, or stavudine)—in the early 1990s. While these medications blocked HIV replication for a short time, it soon became evident that using a single drug, or even two drugs from the same class, allowed the virus to develop resistance.

The next big breakthrough came in the mid-1990s with the approval of the first protease inhibitors, Invirase (saquinavir) and Crixivan (indinavir), and the first non-nucleoside reverse

transcriptase inhibitor (NNRTI), Viramune (nevirapine). This enabled people with HIV and their doctors to put together combination regimens—dubbed highly active antiretroviral therapy, or HAART—that targeted different steps of the HIV life cycle, finally bringing viral replication under control and halting the destruction of T cells.

But the new regimens were not a panacea. Many long-term HIV survivors can remember taking handfuls of pills multiple times a day with complex food requirements. The drugs sometimes caused difficult side effects, including unexpected metabolic problems. What's more, the early meds were not always able to fully control the virus. The Department of Health and Human Services issued its first antiretroviral treatment guidelines in 1998, and over the next several years, experts raised and lowered the threshold for starting treatment in an attempt to limit adverse effects while preserving immune function.

Given these drawbacks, researchers continued their efforts to develop new medications that were more effective, better tolerated and more convenient. The first single-tablet regimen, Atripla (efavirenz/tenofovir disoproxil fumarate/emtricitabine), was approved in 2006, enabling some people to treat their HIV with 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.

Around the same time, the SMART trial confirmed that taking breaks from treatment in an effort to reduce side effects is a risky strategy. It turned out that some of the problems blamed on the drugs were likely attributable to persistent inflammation, which could be minimized if people start treatment promptly and keep their viral load suppressed.

In 2012, federal treatment guidelines recommended that everyone diagnosed with HIV should start antiretroviral therapy right away, regardless of their CD4 count. The START trial, which showed that early treatment initiation leads to better outcomes, validated this approach.

Innovations also continued in the prevention field. As early as 1994, researchers showed that treating pregnant women and their newborns with Retrovir could prevent mother-to-child transmission of HIV. Later research showed that people on effective antiretroviral therapy with an undetectable viral load do not transmit HIV to their sex partners, a concept now known as treatment as prevention, or Undetectable Equals Untransmittable (U=U). Studies also showed that taking antiretrovirals before sex could prevent HIV acquisition, leading to the approval of Truvada (tenofovir disoproxil fumarate/emtricitabine) for pre-exposure prophylaxis (PrEP) in 2012.

Does Your Treatment Measure Up?

Modern antiretroviral therapy is generally effective, well tolerated and easy to use, but that hasn't stopped the quest for new and better options.

There are several reasons you might consider a new regimen, including persistent detectable viral load or inadequate CD4 cell recovery, side effects and difficulty taking your medications consistently. Or maybe you simply want a new regimen that has a lower pill burden or requires

less frequent dosing.

Most people who are starting treatment for the first time, and those who already have an undetectable viral load on a modern regimen and wish to switch for other reasons, will have a range of choices. Biktarvy, for example, is a single-tablet regimen containing a potent integrase inhibitor (bictegravir) and a newer formulation of tenofovir (tenofovir alafenamide, or TAF) that is easier on the kidneys and bones. Another potent integrase inhibitor, dolutegravir (sold alone as Tivicay and a component of the Triumeq, Juluca and Dovato combination pills), can keep HIV suppressed with just one other drug, instead of a standard three-drug regimen.

Finding an optimal regimen is more challenging for people who have been living with HIV for a long time, have extensive treatment experience and whose virus has developed resistance to multiple medications (known as multidrug-resistant HIV).

Such individuals may benefit from novel antiretrovirals that target different steps of the HIV lifecycle. These include Rukobia (fostemsavir), the first HIV attachment inhibitor, and Trogarzo (ibalizumab), a monoclonal antibody that binds to the CD4 receptor on T cells and blocks viral entry. Sunlenca (lenacapavir), the first HIV capsid inhibitor, was approved in December 2022. It is administered by injection once every six months in combination with an optimized background regimen.

Long-acting therapies are the wave of the future for HIV treatment. Sunlenca is now the longest-acting medication, but it must be used with daily pills, and it is only approved for heavily treatment-experienced people with multidrug-resistant HIV.

Cabenuva (injectable cabotegravir and rilpivirine), the first—and so far the only—complete long-acting regimen, was approved in January 2021. Administered by a health care provider once monthly or every other month, it is approved for people wo are currently on a stable regimen with an undetectable viral load. However, recent studies show that it may also be effective for people starting treatment for the first time, and researchers are working on new formulations that could potentially be self-administered. Injectable cabotegravir alone (Apretude) is a long-acting option for HIV prevention.

The bottom line is that HIV treatment has come a long way in the past three and a half decades. With a plethora of highly effective and well tolerated options now available, most people living with HIV can find a treatment approach that keeps their virus in check and is easy to live with.
