25 Years of HIV Research

The increasing mastery over the virus is one of humanity's crowning achievements.

September 1, 2019 By Benjamin Ryan

When POZ magazine was founded in 1994, the U.S. AIDS crisis was just reaching its peak. By the following year, half a million Americans had been diagnosed with the disease and nearly two thirds of them were already dead. And so, marrying the take-no-prisoners activism of ACT UP with the tenacious truth-seeking of a countercultural publication, POZ's scrappy staff and cadre of writers armed themselves with the power of the pen against a potentially indefinite holocaust.

Then came a miracle. In 1996, the first effective combination regimens to treat HIV became available, kick-starting the Lazarus era of the epidemic practically overnight. This reprieve was 15 years in the making—AIDS was first officially identified in 1981—and was the result of the dogged efforts of activists and scientists who were determined to outsmart one of the most destructive and wily viruses to affect the human race.

For a quarter-century now, POZ has provided readers a front-row seat to an astonishing parade of scientific advancements—as well as humbling setbacks—in the worldwide effort to control the global HIV pandemic. It's no hyperbole to claim that the ever-refined collective mastery that scientists have gained over the virus during this period represents one of the all-time greatest achievements of human ingenuity.

But the great work is only beginning. Quality of life for people living with HIV has certainly improved, but the challenges the thousands of HIV researchers toiling around the globe still face are mammoth and sprawling. Vanquishing this particular virus is not merely a matter of developing effective treatments, preventives, vaccines and cure therapies. Epidemic-ending success will require solving the byzantine sociocultural and geopolitical puzzles of how a microscopic sphere encasing a collection of RNA could exploit the myriad weaknesses and faults of societies in order to infect some 77 million people to date, killing nearly half of them.

If the past 25 years of scientific advancements in this field are any guide, the future looks bright.

Coverage from the April 2003 issue

Drug Development

Today, the bedrock of the fight against HIV is the healthy crop of 28 approved antiretrovirals (ARVs) that fall into five classes as well as the 13 single-tablet regimens (STRs) that require only once-daily dosing. For those with multidrug-resistant virus, the antibody therapy Trogarzo (ibalizumab) recently became available. Additionally, HIV regimens may include either of two "boosters," Norvir (ritonavir) and Tybost (cobicistat), which increase the levels of ARVs in the body.

During the contrastingly impoverished early 1990s, hopes that the paucity of ARVs available at the time would significantly extend the lives of people with AIDS were progressively dashed. It turned out that treating HIV with only one or two medications from the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) class—the first, Retrovir (zidovudine, or AZT), was approved in 1987—wasn't enough to beat back the virus. In fact, such treatment often wound up spawning viral resistance to the medications, thus narrowing an individual's future treatment options.

Then, in December 1995, the Food and Drug Administration (FDA) approved Invirase (saquinavir), the first protease inhibitor. In June of the following year, Viramune (nevirapine) hit the market as the first non-nucleoside reverse transcriptase inhibitor (NNRTI). Finally, HIV clinicians could prescribe "cocktails" of three ARVs, which proved to be enough of a multipronged assault to render the virus undetectable in the body—as confirmed by the newly approved viral load test.

Between 1996 and 1997, AIDS deaths plummeted 47% in the United States.

The rub was that some of those ARVs were highly toxic and caused devastating side effects, such as lipodystrophy and diabetes. Additionally, treating HIV required taking numerous pills per day according to rigid schedules and onerous food-intake protocols. Such burdens compromised people's adherence to their ARV regimens, which in turn fueled viral rebound and resistance.

The 2000s brought increasing relief as newer drugs proved ever more tolerable and simpler to take and required less strict adherence to keep viral resistance at bay. Atripla (efavirenz/tenofovir disoproxil fumarate/emtricitabine) was approved in 2006 as the first STR. The following year, the FDA green-lit Isentress (raltegravir), the first of the highly potent and well-tolerated integrase inhibitors.

Thanks to these pharmaceutical advancements and improvements in the overall care of people with HIV, life expectancy for those on ARV treatment today is approaching normal. Nevertheless, researchers continue to refine and improve the HIV treatment tool kit.

The past two years have seen the first STRs that include only two ARVs: Juluca (dolutegravir/rilpivirine) and Dovato (dolutegravir/lamivudine). A long-acting injectable regimen, dosed monthly, will likely gain approval in late 2019. And further down the road, long-acting antibody treatments might require dosing as seldom as two to four times per year.

Coverage from the October 1998 issue

The Treatment-Initiation Conundrum

At the dawn of the triple-combination ARV era, “hit early, hit hard” was the defining treatment ethos—influenced, in part, by a faulty belief that long-term fully suppressive therapy would eventually cure HIV. In 1998, the Department of Health and Human Services (HHS) recommended starting ARVs once an individual’s CD4 count had dropped to 500 or below.

Three years later, in an effort to spare people with HIV the devastating side effects of those early ARVs as much as possible and also to mitigate the emergence of drug resistance, HHS did an about-face. The agency now advised ARV treatment only after CD4s had dropped to an AIDS-defining 200 or lower.

During these trying times, various studies found that people could take periodic breaks, known as drug holidays, from their ARV regimens without lasting immune-system damage. The randomized controlled SMART study, launched in 2002, aimed to confirm such findings using gold-standard research. But in 2006, the landmark trial was terminated years ahead of schedule because it had become evident that drug holidays were actually associated with a higher risk of HIV disease progression and death.

SMART’s stunning findings rocked the HIV research world, in particular because of the discovery that interrupting treatment fueled harmful inflammation—which is itself associated with various health risks. The study ultimately set the stage for the randomized controlled START trial, which began in 2011 and sought to determine whether there was a net health benefit to beginning ARVs with CD4s above 500 versus waiting until the count declined to 350 or below.

In an episode of randomized-controlled-trial déjà vu, the START administrators canceled that study’s deferred-treatment arm in 2015, more than a year ahead of schedule. Going on HIV treatment early, it had already become clear, reduced the risk of AIDS-defining illnesses and other serious maladies. (The trial continues to monitor participants to assess any differences in long-term health outcomes between those who started treatment immediately and those who did so on a delayed basis.)

Upon the START trial’s release, HHS, which had raised the CD4 threshold for an ARV initiation recommendation to 350 CD4s in 2008 and then to 500 CD4s in 2010, promptly advised universal treatment.

After two decades, the HIV treatment protocol had come full circle.

Pre-exposure prophylaxis coverage from the October/November 2014 issue

Prevention

Most of the HIV prevention modalities developed since the early years of the epidemic, when condoms were the only option, are based upon what's known as the biomedical prevention of HIV—the use of medications to thwart transmission.

A major study released in 1994 found that giving AZT to pregnant women with HIV prevented mother-to-child transmission of the virus. Not long after that drug's 1987 release, health care workers began taking a course of ARVs following a potential exposure to HIV on the job.

By 2005, enough research supported the use of post-exposure prophylaxis (PEP)—in which an individual starts a month of a triple-ARV regimen within 48 to 72 hours of a potential exposure to HIV—for the Centers for Disease Control and Prevention (CDC) to finally expand its PEP guidelines to include sexual as well as occupational exposure.

Research findings from the mid-1990s indicated that providing clean needles and syringes to people who inject drugs through syringe services programs reduced their risk of HIV.

Beginning in 2011, a trio of major studies, HPTN 052, PARTNER and Opposites Attract, released a progressive avalanche of data supporting the hypothesis that successful HIV treatment prevents transmission. By the time PARTNER announced findings from its second phase in 2018, a global scientific consensus had solidified: People with HIV who maintain an undetectable viral load cannot transmit the virus through sex.

Undetectable Equals Untransmittable coverage from the March 2019 issue

Meanwhile, in 2010, the randomized controlled iPrEx study found that HIV-negative people who took Truvada (tenofovir disoproxil fumarate/emtricitabine) as pre-exposure prophylaxis (PrEP) greatly reduced their HIV acquisition rate. Researchers would subsequently estimate that daily use of the tablet cuts the risk of HIV by more than 99% among men who have sex with men (MSM) and by at least 90% among women. More recently, the French IPERGAY study confirmed that taking Truvada doses only during the 72-hour period surrounding the time of sex is also highly effective as PrEP for MSM.

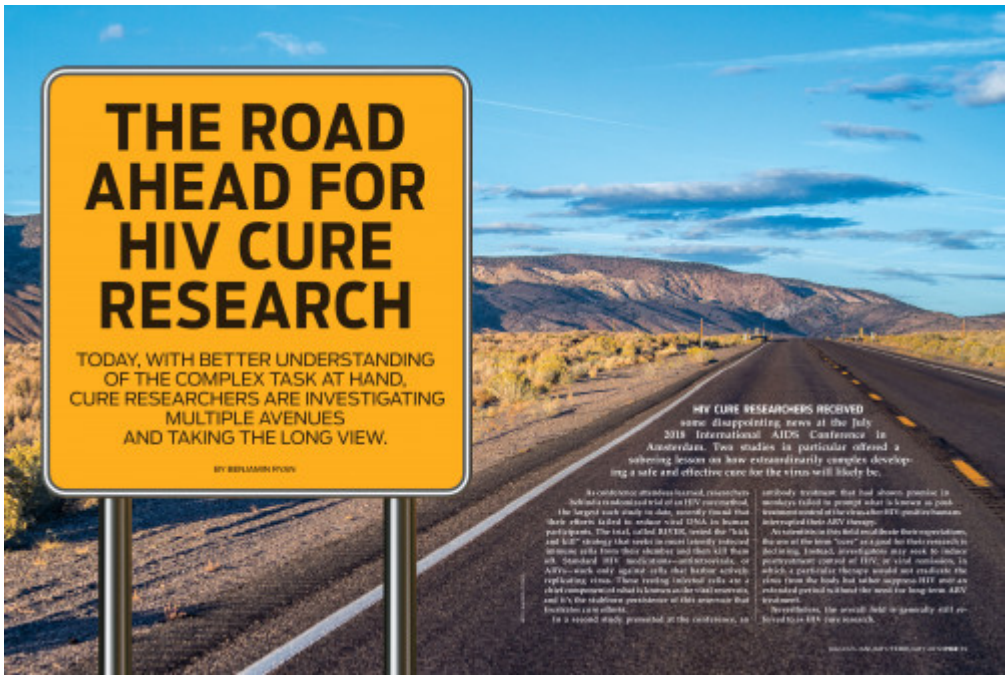
By the end of 2019, the FDA will likely approve a new PrEP option: Descovy (tenofovir alafenamide/emtricitabine), which has the same components as Truvada but with an updated version of the drug tenofovir that is linked to improved markers of bone and kidney health. (It is not known whether using Descovy over Truvada would actually prevent fractures or kidney disease.) A long-acting injectable form of PrEP given every eight weeks may also hit the market by about 2023. Researchers are further investigating long-acting antibody shots as PrEP and, much further back in the pipeline, implants that slowly release preventive medication over a period of months.

The quest for an HIV vaccine has proved particularly frustrating, beset as it has been with repeated failures of major research efforts since the first Phase III trial launched in 1998. Only a single late-stage vaccine study—conducted in Thailand and published in 2009—showed any efficacy: a 31% reduction in HIV risk. Investigators have since sought to build on that result and

develop a more potent product. Today, two late-stage trials of vaccines are under way, and experts are hopeful the candidates will prove at least 50% effective—powerful enough to justify a global rollout by the mid-2020s.

A trio of randomized controlled trials conducted in sub-Saharan Africa and published in the mid-aughts found that voluntary medical male circumcision lowered the risk of female-to-male HIV transmission by about 60%. This finding has led to a concerted push to circumcise millions of males throughout the continent, which has been tied to declining HIV rates among both women and men.

After decades of efforts to develop microbicides to prevent HIV—ARV-infused gels, inserts, rectal douches and the like—researchers have suffered numerous stumbles and setbacks and have succeeded with only one product thus far: a monthly vaginal ring. Currently awaiting regulatory approval, the ring provides at least a modest level of protection against the virus. Meanwhile, U.S. funding priorities are shifting away from microbicide research, a change that calls into question the future of other such preventive products in the pipeline.



Cure

In 2008, the news that a man dubbed “the Berlin Patient” and later identified as Timothy Ray Brown had been cured of the virus jolted the once-sleepy HIV cure research field into action. As treatment for his leukemia, Brown had received stem cell transplants from a donor born with a genetic abnormality that rendered his immune cells resistant to HIV.

Coverage of the “Berlin Patient” from the June 2011 issue

Members of the burgeoning HIV cure research field, backed by swelling financial support, are tasked with the challenge of outsmarting a virus that hides in long-lived resting immune cells. Collectively known as the viral reservoir, these latently infected immune cells remain under the radar of standard ARV treatment, which works only on actively replicating cells.

The long road toward achieving some form of widely replicable cure, viral remission or post–ARV treatment control of HIV is currently following several paths. One strategy, called “kick and kill,” seeks to roust latent cells from their slumber and then finesse the immune system into attacking such cells. Another approach involves genetically modifying an individual’s own cells in an attempt to foster an HIV-resistant immune system like Brown’s—but without the need for potentially fatal cancer treatment such as he received. A third tactic is called “block and lock,” the goal of which is to keep latently infected cells in an indefinite resting state so they never wake up and churn out new virus.

Coverage from the April 2002 issue

Other Health Conditions

Even when people with HIV maintain an undetectable viral load on ARVs, they have a higher risk of developing a host of conditions, many of which are related to aging but tend to strike those with the virus at ages younger than those seen among the general population. These health problems, the incidence of which is driven in part by the overall aging of the HIV population, include cardiovascular disease, various cancers, diabetes, high cholesterol and blood pressure, kidney and liver disease, chronic pain, cognitive decline, bone loss and gastrointestinal problems.

Scientists believe that the chronic inflammatory state associated with even well-treated HIV contributes to many of these outcomes. A major ongoing randomized controlled trial called REPRIEVE, set to complete in 2023, is seeking to determine whether prescribing a cholesterol-lowering statin to people with HIV will temper such inflammation and in so doing reduce the risk of cardiovascular disease and various other health conditions as well as the risk of death.

The HIV population has high rates of other risk factors that fuel major diseases, in particular smoking, as well as coinfection with hepatitis B and C viruses (HBV and HCV). Fortunately, newer hepatitis C treatments have made HCV infection readily curable, and HBV is not only treatable but also vaccine preventable.

Additionally, ARVs themselves, especially the oldest ones, have been tied to myriad health problems. Mental illness and substance abuse disorders may also compromise the health and well-being of HIV-positive individuals.

Compounding all these negative impacts, many people with the virus are low-income and struggle with their basic needs, such as accessing proper food and nutrition, housing, transportation, child care and health care.

In response to such complex concerns, research into improving the care and treatment of HIV increasingly takes a cross-disciplinary, holistic approach that seeks to address the totality of each individual’s unique needs. The ultimate goal is to provide the most robust and comprehensive support for those living with the virus in the hope that they don’t just live a long and healthy life but truly thrive throughout the years.

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