Antiretrovirals: A Success Story

Celebrating 20 years of effective HIV treatment

June 24, 2016 By Benjamin Ryan

In early 1996, Jeffrey Pope began getting his affairs in order, straightening out his finances and his home and visiting his parents for what he assumed would be the last time.

“I was preparing to die,” Pope says.

Since his AIDS diagnosis the previous year, he’d seen his CD4 count plunge from a healthy 600 to a precarious 170. He weathered shingles, pneumocystis pneumonia (PCP) and bouts of severe flu. He had to stop working. The antiretrovirals (ARVs) he was taking—either one or two nucle-oside reverse transcriptase inhibitors (NRTIs, or nukes) at a time, as was standard during the early 1990s—didn’t seem to help at all. By April, his 38-year-old heart gave out, and he needed a pacemaker to keep going.

A month later, his doctor put him on a triple combination of ARVs, including the newly approved Invirase (saquinavir), the first drug from a new class called protease inhibitors (PI). With that, Pope joined the legion of people with AIDS who benefited from what’s known as Lazarus syndrome—or a second chance at life.

In July 1996, infectious disease experts from around the world gathered in Vancouver for the 11th International AIDS Conference. In recent years, these gatherings had become bleak affairs, as data painted in stark relief the fact that the handful of NRTIs that had been approved since Retrovir (zidovudine, or AZT) debuted in 1987 were ultimately a feeble line of defense against the fearsome army of HIV swarming throughout an infected human body.

In recent months, data had begun to surface suggesting that new ARVs emerging from the pipeline just might allow clinicians the means to finally send the virus into retreat.

Vancouver crystallized this vision of the future. A handful of PIs were under investigation at that time and would soon join Invirase on pharmacists’ shelves. Plus, the first non-nucleoside reverse transcriptase inhibitor (NNRTI, or non-nuke), Viramune (nevirapine), had been approved in June. Now, researchers could finally combine three ARVs at once, attacking the virus at multiple points in its life cycle. Numerous presentations at the conference showed that triple-drug cocktails had the awesome capacity to beat HIV down to undetectable levels and keep it there, allowing CD4s to rise. And there was evidence—longer-term, follow-up data confirming stunning findings presented

at a major conference in January—that triple-combo treatment with the PI Norvir (ritonavir) was associated with a reduced risk of death.

The very ability to directly track viral replication was groundbreaking. Before the introduction of viral load testing in 1996, HIV's progress was measured in illnesses, dwindling CD4s and ever-mounting mortality; the AIDS death rate in the United States had soared to more than 40,000 lost to the disease per year.

"Is this the light at the end of the tunnel that we've always been looking for?" Waafa El-Sadr, MD, MPH, a professor of epidemiology at Columbia University, asked herself at the conference.

During those desperate times, El-Sadr would regularly scan the waiting room on her clinic days to see whether any of her HIV-positive patients were looking run-down—a sight that would give her "a horrible sense of doom."

After Vancouver, as her patients gained access to the triple-ARV cocktails, El-Sadr recalls, "Almost rapidly, between one day and the next, I didn't need to glance at the waiting room, because everybody looked well. Now the waiting room was buzzing with energy and hope."

The U.S. AIDS death rate tumbled 47 percent between 1996 and 1997, knocking the disease out of the top 10 causes of death in the country for the first time since 1990. By 1998, an estimated 16,000 HIV-positive people were still living who would not have been so fortunate had the mortality rate continued on its previous trajectory.

As for Pope, who is now 58 and and living in Tallahassee, Florida, his health steadily improved to the point that six months after starting his triple-drug cocktail, he no longer felt that he was about to die.

But there was a big catch: The side effects of the ARVs were so dreary that his actual quality of life was still highly compromised, to say the least.

"Hit early, hit hard" was the HIV treatment ethos during the late 1990s, as coined by David Ho, MD, scientific director of The Aaron Diamond Research Center, who was named Time magazine's man of the year in 1996 for his instrumental contributions to the development of combination ARV treatment. Ho was among those who then believed, wrongly, it turned out, that suppressing HIV with ARVs over the long term could eventually eradicate the virus.

When the U.S. Health and Human Services issued its first HIV treatment guidelines in 1998, the agency recommended ARVs for those with a CD4 count of 500 or below.

Hit hard those ARVs did. "These medications that are saving my life are killing me," Pope repeatedly told his doctors in those days. His drug regimen saddled him with chronic nausea, lethargy and an overall malaise.

Included in the laundry list of other toxic effects linked to the early combination ARV arsenal were peripheral neuropathy, diarrhea, liver and kidney disease and lactic acidosis. Then there was metabolic syndrome, including high blood pressure, blood sugars, triglycerides and cholesterol, which together increase the risk of stroke, cardiovascular disease and diabetes.

“You were alive, but you certainly weren’t well,” says Lynda Dee, cochair of the Fair Pricing Coalition, whose husband died of AIDS-related illness in 1987 and who lost more than 150 friends to the disease.

Perhaps most devastating, a condition known as lipodystrophy, which is closely linked to metabolic abnor-malities, led to disfiguring, typically permanent changes in the fat distribution in many people taking triple-ARV cocktails. (Retrovir, Zerit [d4T, or stavudine] and Videx [ddI, didanosine] are now considered the culprits and consequently are seldom used today.)

Fat disappeared from the face, limbs and buttocks while accumulating around the organs, in the breasts and on the upper back and neck. The changes left individuals instantly recognizable as HIV positive to those in the know and appearing ill to others.

“My face melted,” says Pope. “My arms and legs melted. They were just gone.”

Adding insult to injury, pharmaceutical advertisements during this era painted a notoriously rosy image of life on ARV treatment. Typical HIV medication ads depicted robustly healthy models climbing mountains, enjoying a bike ride or sailing. In 2001, the U.S. Food and Drug Administration (FDA) sent a stern letter to the major HIV drug manufacturers, criticizing them for downplaying the toxic reality of life on ARVs and telling them to clean up their acts.

Adhering to the byzantine complexity of the typical drug regimen was yet another daunting challenge.

“I used to take care of people, and they’d have like 28 pills a day that they’d have to take multiple times: before meals, after meals, with fluid, without fluid, before they go to bed, when they wake up,” says Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases. “It was very disruptive to your life.”

There was little room for error in this calculus. Even a slight dip in adherence to the early HIV cocktails could allow the virus to replicate enough to develop resistance to ARVs. People like Pope who had been treated ineffectively with only one or two HIV drugs at a time were often haunted by the fact; before the advent of triple-combo therapy, their virus often developed resistance, which ultimately limited their treatment possibilities.

Pope became resistant to all available HIV medications almost as fast as the pharmaceutical industry could develop them. By 2002, he ran out of options and his doctor took him off treatment entirely; the drugs weren’t doing him any good anyway. He went back to presuming he would die. But then in 2003, the injectable drug Fuzeon (enfuvirtide), representing a new class of ARVs as the first-ever entry inhibitor, came along and his life was saved yet again.

By 2001, the U.S. HIV treatment guidelines did AN about-face, recommending ARVs only once a person's CD4s dropped to 200 (previously, the cutoff was 500 CD4s). People with HIV and their clinicians alike were often eager to rationalize delaying therapy in order to avoid ARVs' toxicities.

Enter the structured treatment interruption. Many small studies had found that allowing people to go off their ARVs for a period gave them a much-needed break from toxicities without allowing the virus to do significant harm to their immune system. However, because none of these studies were randomized controlled trials, they could not provide gold-standard scientific proof to back up their findings.

To definitively answer whether treatment interruptions guided by individuals' CD4 counts reduced the risk of sickness and death, a vast team of researchers established the SMART trial, a global study that in 2003 began enrolling a planned 6,000 people with HIV with a CD4 count of at least 350. The participants were randomized either to take ARVs continuously or to follow an episodic treatment protocol: go off or stay off treatment until their CD4s hit 250, then take ARVs until their CD4s reached 350 and then start the treatment interruption process again. Keeping the participants in this window was considered safe because at the time, CD4 count was considered a reliable indicator of the risk of health complications.

SMART was meant to run for seven or eight years. However, in a stunning development, the trial was ter-minated in January 2006 after it became abundantly clear that the treatment interruption strategy could be quite harmful, even fatal. The landmark findings, which shook up the HIV research agenda, shaping it for a decade to come, were published later that year. Compared with those on continuous treatment, the participants who took drug holidays had a greater risk of death, opportunistic disease and major cardiovascular, kidney and liver disease.

The SMART researchers went back to stored blood samples from the study's participants, and as they looked at various markers of inflammation and coagulation, they began connecting the scientific dots. They found that such markers rose during treatment interruptions and that several of them were associated with risk of death, even among those still on treatment who had a suppressed viral load. Their findings would inspire a new quest in the HIV research field: to understand how the chronic inflammatory state that HIV infection apparently prompts may fuel various diseases associated with aging.

Considering the dangers associated with a freely replicating virus, researchers shifted their focus to determining the optimal point at which to start someone on ARVs.

During the 2000s, HIV treatment became progressively less toxic, more potent and easier to take, with vastly reduced pill burdens and simplified food restrictions. In 2006, the approval of Atripla (efavirenz/tenofovir disoproxil fumarate/emtricitabine) ushered in a new treatment era in which one pill once a day was all many people needed to suppress the virus. Today, there are six such tablets on the market.

New drugs, as well as a new drug class, broadened the choices for those first starting treatment while permitting individuals who were failing treatment to go on regimens different enough from their old drugs that they could still suppress the virus.

In 2007, Isentress (raltegravir) became the first of three highly tolerable integrase inhibitors—a class of ARVs that has allowed for the construction of both NNRTI- and PI-sparing regimens—to get the green light.

The newer HIV regimens have more dosing "forgiveness," meaning adherence doesn't have to be as strict as with older treatments to maintain full suppression of the virus.

During the 2010s, research established that ARVs have the power not only to prevent disease but also to block HIV transmission. (Of course, scientists had shown in the mid-1990s that HIV treatment prevents mother-to-child transmission.) At the beginning of the decade, the global iPrEx study proved that a daily regimen of Truvada given to HIV-negative men who have sex with men reduced their risk of contracting the virus; further research would estimate that daily adherence lowered the risk by more than 99 percent. The FDA approved Truvada as pre-exposure prophylaxis (PrEP) for high-risk groups in 2012.

In 2011, the famed HPTN 052 study found that when the HIV-positive members of mixed-HIV-status hetero-sexual couples started ARVs, they reduced their risk of transmitting the virus by 96 percent. More recent research has suggested that the risk of passing on HIV with an undetectable viral load for both anal and vaginal sex may in fact be zero.

"HPTN 052 became a watershed moment where we started to think about HIV treatment not only as something that was associated with these profound individual benefits," says Tim Horn, HIV project director at Treatment Action Group, "but some-thing that was associated with profound public health benefits."

Amid such excitement, a concerted faction within the HIV community became concerned that public-health-level goals were subverting the medical autonomy of those considering treat-ment for the virus.

Meanwhile, repeated studies had found that starting ARVs with a high CD4 count was preferable to waiting until they dropped. And by 2012, U.S. treatment guidelines, after raising the treatment initiation CD4 threshold to 350 in 2008 and 500 in 2010, recom-mended universal treatment regardless of CD4 count. But some clinicians, wary that the science backing early treatment wasn't gold standard, held out against the policy shift, wanting more definitive proof.

The START trial sought to provide such an answer. Begun in 2011, the randomized-controlled trial included 4,685 people with HIV across the globe who were randomly assigned either to start ARVs with more than 500 CD4s or to wait until their count dropped to 350 or below. In 2015, START's placebo arm was terminated more than a year early when evidence mounted that early treatment was preferable. Compared with delaying, starting ARVs early reduced the risk of AIDS-defining illnesses as well as serious non-AIDS illnesses.

Since the desperate early years of the epidemic, drug development has transformed HIV from an almost certain death sentence to a man-age-able disease, one treated with increas-ing ease. Along the way, life expectancy for people on ARV treatment has risen steadily and by some measures is now approaching normal, in particular for those who start treatment with more than 500 CD4s, don't have hepatitis B or hepatitis C, and don't abuse drugs or smoke.

"When I talk to my colleagues in other fields, they marvel at how fast things have moved in HIV," says James D. Neaton, PhD, a professor of bio-statistics at the University of Minnesota, who along with Waafa El-Sadr was a cochair of the SMART trial.

In the words of Anthony Fauci, "The progress has been breathtaking."

Which is not to say that researchers can call it a day. Numerous factors still compromise the overall health of people taking ARVs, including the conse-quences of the chronic inflammatory state that can persist even when a viral load is undetectable, existing medica-tion toxicities and hepatitis B and C coinfection. The population is at an elevated risk for cardiac, kidney and liver complications and various non-AIDS-defining cancers.

Plus, there is the sheer inconvenience of having to take ARVs every day.

For Jeffrey Pope, life remains a careful balancing act. Beset by numerous health problems, including heart disease and diabetes, he has remained retired from a career as a medical systems engineer since first facing death 20 years ago.

"I'm glad to be alive," he says, "but I feel like I have been through a war. And the war goes on. I strive to find grace in everyday life."

The ARV ABCs

The drugs in each class combat HIV at a different phase of its life cycle.

- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs, or nukes)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs, or non-nukes)
- Protease inhibitors (PIs)
- Entry inhibitors
- Integrase inhibitors

Additionally, Tybost (cobicistat) and Norvir (ritonavir) are boosters used to raise the level of ARVs in the body.

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