A Shot in the Dark

We got COVID-19 vaccines in record time. Why are HIV vaccines taking so long?

March 29, 2021 By Liz Highleyman

In March 2020, as a new pandemic swept across the globe, National Institutes of Allergy and Infectious Diseases (NIAID) director Anthony Fauci, MD, predicted that a COVID-19 vaccine could be available in 12 to 18 months. A year later, three highly effective vaccines are authorized in the United States, and over 95 million Americans have received their first dose.

In April 1984, Health and Human Services Secretary Margaret Heckler predicted an HIV vaccine could be ready for testing in two years; 37 years later, we're still waiting.

Many people have speculated that if the same level of focus and resources we've seen with COVID-19 had been devoted to HIV, we'd likely have an HIV vaccine by now.

"How deeply I wish we had had a similar commitment by our government and society to fight HIV in the early days, before so many people in my community died," California state senator Scott Wiener wrote in a recent Buzzfeed essay.

But while the early response to AIDS was painfully—some would say criminally—slow, that's no longer the case. A generation of scientists have devoted their careers to HIV science, and HIV now receives more research funding than most diseases.

"My annual budget is $1 billion a year," says Carl Dieffenbach, PhD, director of the NIAID's Division of AIDS. "Over the course of 20 years, it's been about $15 billion. Easily a third of that has gone to HIV vaccine research."

Carl Dieffenbach, PhDCourtesy of Carl Dieffenbach, PhD

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Yet brainpower and money have not been enough. Unlike the quick home runs in COVID-19 vaccine development, dozens of HIV vaccine candidates have shown promise in laboratory and animal studies, only to fail in clinical trials.

There are many reasons why it's harder to develop vaccines for HIV than for the SARS-CoV-2 coronavirus.

First, a brief immune system overview. The innate immune system kicks in first, launching a nonspecific attack against invaders. Then, the adaptive immune system comes into play to

respond to specific pathogens. B cells produce billions of different antibodies, which bind to foreign proteins called antigens like a lock and key. CD4 helper T cells coordinate the immune response, while CD8 killer T cells attack invaders. After the threat subsides, a subset of memory B cells and T cells remain on guard to fight the same invader in the future.

Preventive vaccines teach the immune system to fight an invader it hasn't yet encountered. Traditionally, they contain a weakened version or pieces of a pathogen. A vaccine can either confer sterilizing immunity, which prevents a pathogen from gaining a foothold in the body, or it can work soon after infection to stop the pathogen from causing illness. The latter approach is difficult with HIV because the virus establishes a permanent reservoir and starts to do its damage within a few days after infection.

HIV mutates frequently as it replicates, producing countless variants. Over time, distinct HIV subtypes have emerged in different regions of the world—for example, subtype B in North America and subtype C in Africa. What's more, the HIV spike protein, which attaches to cells, is covered with sugar molecules that provide camouflage.

"HIV is a very wily adversary," says Susan Buchbinder, MD, director of Bridge HIV at the San Francisco Department of Public Health and a member of the HIV Vaccine Trials Network (HVTN) executive committee. "It mutates rapidly, so there's quite a bit of variability. It has a glycan shield that protects the viral envelope. And once it becomes established, it creates a chronic, lifelong infection that can't be cleared."

Susan Buchbinder, MDCourtesy of Susan Buchbinder, MD

But perhaps most important, people usually don’t develop strong natural immunity against HIV. A small number, known as elite controllers, do mount a robust immune response, but this is rare, and researchers have not figured out how to mimic it in others.

People with HIV do produce antibodies, but they usually target parts of the virus that are highly variable, so they don’t recognize new mutations. A few people naturally produce broadly neutralizing antibodies (bnAbs) that target hidden, conserved parts of the virus that don’t change much. Researchers are developing bnAbs for HIV prevention and treatment, but the holy grail is a vaccine that can teach the immune system to produce its own bnAbs.

“A vaccine generally mimics the body’s natural immune reaction to a virus, which usually results in it being cleared,” Fauci says. “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.”

Multiple Approaches

Many strategies have been explored in the quest for an HIV vaccine. The earliest candidates took a traditional approach, injecting viral proteins to trigger antibody production.

AIDSVAX, the first vaccine tested in Phase III clinical trials, contains gp120 envelope proteins from different HIV strains. In 2003, researchers reported that the vaccine offered no significant protection compared with a placebo, and there was no difference in viral load among those who did become infected.

Some researchers then turned to T-cell strategies. Although using weakened HIV is too dangerous, other viruses can be engineered to carry HIV genes or proteins to trigger T-cell immunity.

The Phase IIb STEP trial (HVTN 502) evaluated a vaccine that uses an inactivated adenovirus type 5 common cold virus to deliver three subtype B HIV proteins. After early studies showed that the vaccine triggered HIV-specific T-cell responses, STEP enrolled more than 3,000 volunteers in North America, South America and Australia. (see “Hit Me With Your Best Shot,” below.)

But the study was halted ahead of schedule in 2007, after an interim analysis found that the vaccine did not reduce the risk of acquiring HIV. Even worse, uncircumcised men and people with higher levels of preexisting antibodies against adenovirus 5—which is common worldwide—were more likely to contract the virus. The Phambili trial (HVTN 503), which tested a similar vaccine with subtype C HIV proteins in South Africa, was also discontinued.

As with HIV treatment, many experts thought a combination approach would work better, using one type of vaccine as a primer and a different type as a booster.

The RV144 trial in Thailand tested a modified version of AIDSVAX plus ALVAC-HIV, which uses a canarypox vector to deliver DNA for HIV proteins. This was a controversial approach, since neither component worked well alone. But in 2009, researchers reported that this prime-boost combination reduced new infections by 31%—the first, and so far only, direct evidence that a vaccine can prevent HIV. While this may not seem very impressive, experts say that even a 50% effective vaccine could offer a major public health benefit.

The RV144 results left many questions unanswered and sent researchers back to the drawing board to design modified vaccine components and delivery methods.

The Phase II/III Uhambo trial (HVTN 702), which enrolled more than 5,400 men and women in South Africa, tested ALVAC-HIV plus a gp120 protein vaccine, both adapted to HIV subtype C. This study was halted in February 2020 after an interim review found that the HIV infection rates were similar in the vaccine and placebo groups.

The closure of Uhambo leaves just two large vaccine trials underway: Imbokodo (HVTN 705) and Mosaico (HVTN 706). Both are testing a primer vaccine dubbed Ad26.Mos4.HIV that uses an adenovirus type 26 vector. After the failure of STEP, researchers turned to a less common adenovirus that most people have not yet been exposed to. The virus carries a computer-designed mosaic of antigens derived from multiple HIV strains found around the world.

A set of preparatory studies tested Ad26.Mos4.HIV plus various boosters, finding combinations that induce strong antibody and T-cell responses. One of them showed that the best regimen was 67% effective at protecting monkeys exposed to SIV, HIV's simian cousin.

Imbokodo, started in 2017, has recruited more than 2,600 young women at high risk for HIV in southern Africa. Mosaico, started in 2019, aims to recruit 3,800 cisgender gay and bisexual men and transgender people in North America, South America and Europe. Participants will receive either four injections of Ad26.Mos.HIV plus two gp140 protein booster shots or an equal number of placebo injections.

After hitting some snags in 2020 due to COVID-19, Imbokodo is now fully enrolled, and Mosaico has resumed recruitment. Results are expected in 2022 and 2024.

HIV vaccine trials have always offered condoms and risk-reduction counseling, but pre-exposure prophylaxis (PrEP) adds a new wrinkle. It would be unethical to deny participants proven prevention tools, but they make it harder to tease out the effects of a vaccine. Prospective Mosaico participants will be offered PrEP, and only those who decline will be enrolled. The idea, according to Buchbinder, is that the trial will select participants who are looking for a different kind of prevention method.

A bigger issue is that the availability of effective biomedical prevention and antiretroviral therapy, which prevents HIV transmission when viral load is undetectable, have led some to question whether expanding access to these might be a better investment than more vaccine research.

What's in the Pipeline?

Further back in the pipeline, researchers are exploring novel ways to make HIV vaccines more effective.

One avenue involves alternative viral vectors. For two decades, Louis Picker, MD, of the Vaccine and Gene Therapy Institute at Oregon Health and Science University, and colleagues have been working on vaccines that use a cytomegalovirus (CMV) vector. They found that a CMV vaccine carrying SIV proteins induced durable CD8 T-cell responses that protected monkeys exposed to the virus. Although the animals showed evidence of initial infection, half were able to clear the virus. Vir Biotechnology launched the first Phase I trial of a human version of this vaccine (VIR-1111) last December.

A rational vaccine design approach aims to create stabilized versions of the three-pronged HIV spike protein that make the hidden conserved region targeted by bnAbs more visible. Dennis

Burton, PhD, and his team at Scripps Research showed that a vaccine based on one of these so-called SOSIP trimers could delay or prevent infection in exposed monkeys; clinical trials are now underway.

Vaccines using naked DNA, or direct injection of HIV genetic material, have been studied for decades with minimal success, but a process known as electroporation—a small shock that opens cell membranes—makes this approach more feasible.

The messenger RNA (mRNA) technology used in the Pfizer-BioNTech and ModernaCOVID-19 vaccines is also being developed for HIV. This approach uses lipid nanoparticles to deliver genetic instructions for making viral proteins, in effect turning cells into antigen-production factories.

At last year's International AIDS Conference, researchers reported that an experimental mRNA vaccine triggered production of cross-neutralizing antibodies in monkeys. This vaccine carries genes that instruct cells to make virus-like particles; some monkeys also got SOSIP trimer boosters. Of the seven monkeys that received the most effective regimen, three did not become infected with SIV, and infection was delayed in the other four. Moderna and BioNTech are both working on mRNA HIV vaccines.

Several efforts focus on encouraging the immune system to make its own broadly neutralizing antibodies. Most people possess specialized B cells capable of producing bnAbs, but they're few in number—only about one in a million immature B cells. An approach known as germline targeting uses a series of vaccines to train these immature B cells to generate bNAbs in a stepwise fashion. Other researchers are using viral vectors or mRNA to deliver genetic blueprints that instruct other types of cells to build bnAbs, such as VRC01.

HIV Lays the Foundation

The mRNA approach is an example of how basic science can lead to unexpected breakthroughs.

"Advances in HIV vaccine science have literally paved the way for SARS-CoV-2 vaccines," says Fauci. "What goes around comes around, and I expect this to feed back into HIV vaccine development."

The success of the Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines builds on decades of research. And the Johnson & Johnson COVID-19 vaccine employs the same adenovirus platform used in the HIV vaccine being tested in Imbokodo and Mosaico.

"To make a better mousetrap, we have focused on developing really good platforms to deliver viral antigens," says Dieffenbach. "So the adenovirus vectors, the messenger RNA, direct injection of DNA—all of these platforms got their start in HIV."

Just as HIV research has laid the groundwork for COVID-19 vaccines, lessons learned from the new coronavirus could further the quest for HIV vaccines.

"One thing we've seen with COVID is that where there's a will there's a way, and you can cut

through a lot of the red tape that sometimes bogs down these trials," says Buchbinder. "We also saw a tremendous outpouring of altruism on the part of study volunteers who wanted to participate in COVID vaccine research. My hope is that this will transfer over to HIV vaccine research. We need more volunteers who are willing to roll up their sleeves and participate."

[This is an updated and expanded version of a feature in the April-May 2021 print edition of POZ.]

Hit Me With Your Best Shot

Participating in HIV vaccine research can help end the epidemic.

By Liz Highleyman

Before he became known as a proponent of pre-exposure prophylaxis (PrEP), Damon Jacobs, a licensed marriage and family therapist in New York City, put his body on the line to help develop another HIV prevention tool. In 2006, he volunteered for STEP, a study of an experimental HIV vaccine (click here).

Damon JacobsCourtesy of Damon Jacobs

Jacobs, 49, learned about the trial because his partner at the time was a participant. “It made a big difference that I knew someone who had done it and that he could tell me about his experience,” Jacobs says. He later applied that lesson when he started the PrEP Facts Facebook group in 2013: “You need that personal connection.”

Jacobs received three injections of the vaccine. “The experience was a little scary,” he recalls, “but I was just so grateful to be part of the solution.” The drawbacks? “There were a lot of appointments, and that got a little tedious after a while.” Plus, the vaccine triggered antibody production, so he tests positive on standard HIV screening tests and instead needs HIV RNA tests.

Unfortunately, not long after he got his third shot, the study was stopped ahead of schedule after

a preliminary analysis showed that the vaccine did not reduce the risk of contracting HIV.

“It was really disappointing, but we had been told that this was possibly going to happen,” Jacobs says. “Every vaccine we take for granted today was the result of clinical trials, many of which failed. I don’t even think failed is the right word. They had to find out what didn’t work to help them find out what did work.”

His advice for people thinking about a vaccine study? “Learn the facts; learn the science. There haven’t really been any adverse side effects among people participating in HIV vaccine trials. If you care about helping the world and ending HIV, this is a very meaningful way. Literally, your body can help end HIV in our lifetime.

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