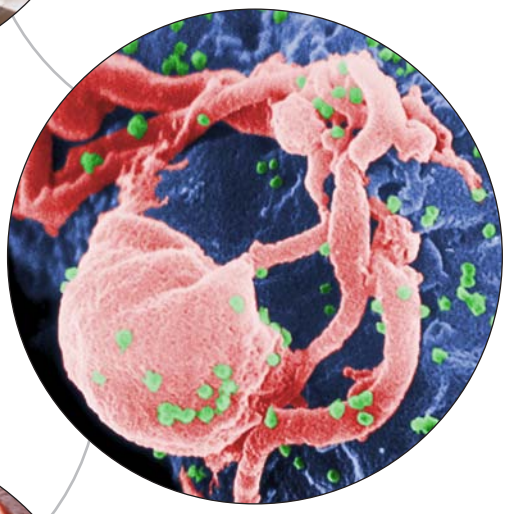
A Living History of AIDS Vaccine Research



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Anthony Fauci has been at the forefront of AIDS vaccine research for decades. When AIDS surfaced in 1981, he, like many other scientists and physicians, was drawn to the mysterious illness, which has now claimed more than 25 million lives—more than the populations of Ghana or Taiwan. Since 1984, he has served as director of the National Institute of Allergy and Infectious Diseases (NIAID) at the US National Institutes of Health (NIH). He has been a key advisor to US presidents on global AIDS issues and was a leading architect of the US President's Emergency Plan for AIDS Relief (PEPFAR). Born on Christmas Eve, 1940, and raised above a pharmacy in Brooklyn, New York, he earned a medical degree from Cornell Medical College. Fauci, a marathoner, avid fisherman, and father of three, has invited AIDS activists into his home. Last year, he presided over a US$4.4 billion budget—roughly a third of it dedicated to HIV/AIDS research.

He ranks among the top 10 most cited HIV/AIDS researchers in the world and has received numerous awards, including the Presidential Medal of Honor for leading the fight against HIV/AIDS and the Lasker Award for Public Service. "I don't see myself as a politician, I see myself as an honest broker of science. That's the reason why I think I've been able to be effective," Fauci said during a January 2009 interview with *IAVI Report* Managing Editor Kristen Jill Kresge and Science Writer Regina McEnery, which served as the basis for this first installment in the Living History series and features Fauci in his own words.

Additional chapters, each featuring a recounting of historic milestones in the search for a vaccine by some of the most prominent players in the field, will appear in upcoming issues.

A video podcast with Fauci can be viewed or downloaded at *www.iavireport.org*

June-July 1981
In a chilling prologue to one of the worst pandemics in human history, the Morbidity and Mortality Weekly Report issues a brief report about an unusual spate of pneumocystis carinii pneumonia (PCP) infections among "five gay, otherwise healthy men" from Los Angeles. Fauci, a young immunologist at NIAID, is instantly curious because PCP has almost exclusively been seen in severely immune-compromised individuals, and these men have no known medical history that could have predicted this unusual diagnosis. A month later, 46 more cases are reported, in Los Angeles, San Francisco, and New York. Those affected are now also developing Kaposi's sarcoma, a cancer caused by a herpes virus, which becomes a hallmark of this new disease.

Fauci: For the first time in my medical career I actually got goose pimples. As more cases were being reported, I decided in the summer of 1981 that I would change the direction of my laboratory and focus only on this unusual disease called at that time Gay Related Immunodeficiency Disease, or GRID. We didn't know it was a virus, we didn't have a virus, but it was acting like a virus, and it was destroying the immune system.

My mentor, Dr. Sheldon Wolff, who recruited me to the NIH, called me and said, 'You're crazy. You have such a great career in front of you. Do me a favor, don't give up your day job.' Well, I did give up my day job, and I essentially went full time studying HIV in the lab until 1984 when I became director of NIAID.

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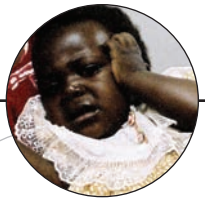


April 23, 1984

Reported cases of the mysterious new disease, now called AIDS, top 4,000 in the United States and reported deaths surpass 1,800. Hemophiliacs, infants born to HIV-infected mothers, and injection-drug users, in addition to men who have sex with men (MSM), are at high risk, and observations of this same disease from sub-Saharan Africa hint at the developing tsunami that would soon overwhelm swaths of the continent. Then-US President Ronald Reagan is criticized for ignoring the burgeoning epidemic. But the public health community is encouraged when scientists in both the US and France announce separately that they have discovered a new retrovirus as the cause of AIDS. At a press conference highlighting the achievements of the US team led by Robert Gallo from the National Cancer Institute, Reagan's Health and Human Services Secretary Margaret Heckler tells the media that a vaccine candidate will be ready for testing within two years.

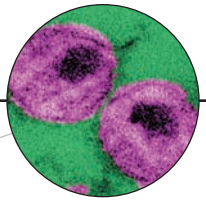
Fauci: Even though it was interpreted that she said we would have a vaccine in two years, she really said we would have a vaccine *ready for testing* in two years. Subsequently, when all of the issues began to emerge about how difficult it would be to get an AIDS vaccine, she suffered slightly justifiably, but mostly unjustifiably, as having predicted that we would actually have a vaccine ready for use and distribution. Two to three years after that announcement, [a trial testing] one of the early, unsuccessful HIV envelope candidates actually started right here at the NIH. It certainly wasn't the right vaccine, but it's just interesting that many years later when you talk about the big gaffe that she made, in reality it wasn't.

Spring 1985

With no drugs or viable vaccine candidates available to treat or prevent the growing epidemic, Fauci approaches then-NIH Director James Wyngaarden about quadrupling funds to jump-start efforts to combat the elusive virus. To handle the escalating research efforts, NIAID later creates the Division of AIDS within NIAID. These moves are criticized by some scientists, but Fauci's decision is later justified as the epidemic evolves into one of the worst in history.

Fauci: We got an extra $60-$100 million, which at the time was an enormous amount of money. A lot of people got angry that the new director of NIAID was putting all of this money into AIDS. Now we're spending, appropriately, $2.9 billion a year at the NIH on AIDS. But at that time people thought this was just a curiosity of a disease and that it would not have a major public health impact, and of course history has shown that that is absolutely not the case.

When you're living through history you often don't realize that what you are experiencing is an historic event. I think if you read the history books and you see people who are involved in things that ultimately turn out to be historic, rarely did they realize that what they were doing was something historic. We are living through one of less than a handful of the most devastating pandemics ever to confront human civilization—pandemic flu of 1918, smallpox, the plague, and HIV. Every year that goes by 2.7 million people get infected with HIV. So there's a lot of passion in wanting to do something about it.



June 17, 1994

HIV's virtually unrivaled ability to mutate makes traditional vaccine strategies, such as the use of live attenuated or killed versions of the virus, both risky and impractical. Instead US biotechnology company Genentech develops an AIDS vaccine candidate comprised of HIV gp120 and approaches NIAID about funding a Phase III trial—the first ever efficacy trial of any AIDS vaccine candidate. But based on the data, Fauci refuses to fund the study.

Fauci: When we were considering this Phase III trial, understandably, there was a lot of play on emotion. How can we sit here and do nothing? That's a very strong reason to push on the empiric approach, and I wasn't against that, but I was starting to realize that the scientific data was really weak.

In general, classical vaccinology is based on the premise that we see what the body does in natural infection and we try to mimic it. We were focusing on the classic paradigm, which is understandable, because that's how vaccines have been developed for decades. But, as we were developing AIDS vaccines, we started to see that some of those classic paradigms didn't hold. It was very difficult in the natural state to develop neutralizing antibodies. Essentially nobody eradicates the virus from their body. There's a small percentage of long-term nonprogressors who seem to control virus replication, but inevitably the disease progresses and the immune response is inadequate. We still don't know why the immune system is incapable of mounting a response that with any other virus would ultimately be protective.

June 9, 1999

NIAID establishes the Vaccine Research Center (VRC) at the NIH to focus primarily on development of an AIDS vaccine. The VRC is the result of a 1997 pledge from then-President Clinton to develop an AIDS vaccine within 10 years.

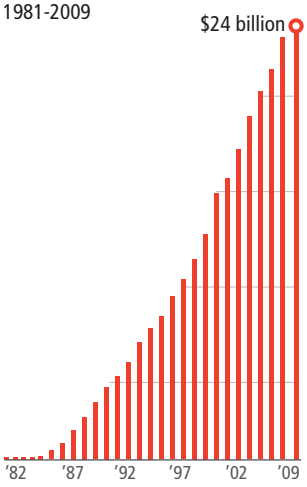
Fauci: Harold Varmus and I, and a few others, went down to the White House and were briefing Vice President Al Gore and President Bill Clinton about HIV/AIDS. I was actually showing him a now-famous picture of me explaining what CCR5 is and how the virus binds to CD4 and then changes its conformation and goes to CCR5. I told him this has really important relevance for the development of a vaccine because it's those cryptic and then exposed epitopes that we can't seem to make a good immune response against. And as we were walking out to the Rose Garden, the president said, 'So what is it that you really need?' I said, we need to accelerate our effort on vaccine development and the best way we can do that is to have an entity where we can go from fundamental basic research right up to the early phases of testing. If we can get a critical mass of the best people in one place physically, first here on campus and then perhaps even in the extramural community, that would be a big contribution. So they said, 'Do it.' It was the fastest time from somebody promising us a building to actually getting it.

October 1, 2002

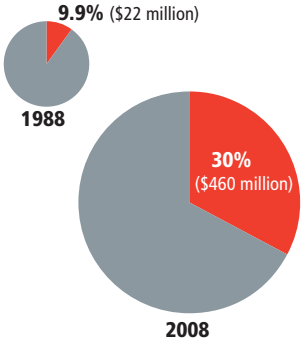
NIAID assumes control of the US Department of Defense's HIV Research and Development Program, which had been preparing for a Phase III efficacy trial in Thailand to test Sanofi Pasteur's canarypox-based vaccine candidate in a prime-boost combination with a gp120 candidate developed by VaxGen. Many researchers publicly criticize NIAID's eventual decision to move ahead with this trial since there was little evidence that this prime-boost strategy would be effective.

Fauci: I think the scientific data [with this prime-boost strategy] was a little bit stronger [than for just gp120]. In a perfect world, if there were not commitments that had been made to other nations and to other agencies, the decision may have been different. When that decision was made, we were learning more about how problematic this virus is. At the same time there was a push, driven by the historic success of empiric approaches and the compelling need in certain countries for a vaccine. It's critical to understand that. You have a country that says, 'You people promised you would help us with this vaccine. We know the chances might be slight, but slight is better than nothing.' There were a lot of people who were saying in a very objective way—I felt somewhat that way myself—that this has a really small chance to be successful. But you've got to balance that against other issues. Would I have done a trial like that in the US? No way, because the infection rate in the United States is significantly lower than what it was at the time in Thailand.

Federal Funding for HIV/AIDS
1981-2009



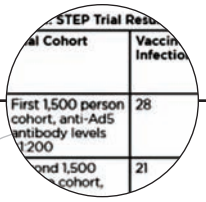
NIAID AIDS Vaccine Funding
As a percentage of NIAID AIDS funding



Source: NIAID

July 14, 2005
NIAID announces $300 million in funding over seven years to establish a virtual consortium of research laboratories known as the Center for HIV/AIDS Vaccine Immunology (CHAVI). The Center was based on recommendations by the Global HIV Vaccine Enterprise that Fauci and 23 other AIDS researchers proposed two years earlier to better coordinate research and promote big science efforts to overcome key immunological roadblocks to vaccine development.

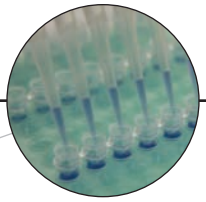
Fauci: Even at the time that we were doing empiric clinical trials, the science was evolving and we were realizing that there were so many things that we needed to discover. So we came up with some recommendations, which were ultimately published in a now very well-quoted article in *Science*. One of the things that we recommended was to have centers modeled in an extramural and collaborative way, like what we had done with the VRC, and that one of the centers would be involved in immunology since it's such an important component. When the center came about, a number of people said we were putting in too much money, which is very interesting because many of those people were in on the recommendation that we should have this kind of center. I think, at the end of the day, most people feel that CHAVI is very productive.



September-November 2007
A large Phase IIb proof-of-concept trial of 3,000 individuals known as STEP shows Merck's adenovirus serotype 5 (Ad5) vector-based vaccine candidate (MRKAd5) is not effective. Subsequent findings, released two months later, suggest the vaccine might have led to an increased susceptibility to HIV among uncircumcised men with pre-existing immunity to the Ad5 vector. The results of the trial are a major disappointment to many and highlight some of the major gaps in AIDS vaccine strategies. Fauci first learns the results of the STEP trial when he receives a phone call from Larry Corey, principal investigator of the HIV Vaccine Trials Network.

Fauci: Larry sounded like he had been hit by six trucks. I've never heard him sound so bad. He said, 'Tony, you're not going to believe what I'm going to tell you. There's nothing there. Not even a hint or a whiff of any effect. And brace yourself, it looks like there may even be an increased risk among some of the people—particularly those with high adenovirus titers.' Although some of us, myself included, were really less than cautiously optimistic, we were hoping that we would see some signal that would allow us to build on the next generation of a similar type of vaccine. We didn't expect that the first look at the data would show essentially abject lack of success, as well as a spectre of risk.

My job was to remind people that research is fundamentally a bunch of failures with an occasional bright light of a success and to tell them that we're not going to give up on vaccines.



March 25, 2008
The STEP trial, which was funded in part by NIAID, sets the field on a new course and sparks debate about the prospects of T-cell based vaccine candidates. NIAID announces plans to shift funding from product development to basic discovery at a daylong Summit on HIV Vaccine Research and Development.

Fauci: There were some people who were inappropriately saying we might as well not do any vaccine research. That's the absolute wrong response. Not only are we not going to stop HIV vaccine research, we're actually going to accelerate it and put more money into it, however, we're going to take a look at what we're doing. So we brought in a group of people who had been laboring at this for some time, as well as some people with new ideas. Since natural infection hasn't proved the concept we've got to do better than natural infection. The days of the empiric, give me a product and I'll test it in a big trial, essentially are over. That doesn't mean that clinical trials are over because clinical research and clinical trials can be part of discovery. Small trials that look at immune responses, the nature of the response, and its breadth and depth, those things are part of discovery.

July 17, 2008
In the immediate aftermath of the STEP results, several planned trials are postponed. One of these, known as PAVE 100, was a Phase IIb test-of-concept trial of a DNA/Ad5 prime-boost regimen developed at the VRC. Following the STEP trial results, the PAVE 100 trial protocol was altered to include only circumcised MSM in the US with no pre-existing Ad5 antibodies, but Fauci decides the data is insufficient to support a trial of this size and scope. A protocol for an even smaller trial is still under consideration.

Fauci: PAVE was different in several ways from STEP. First of all, it [the Ad5-based candidate] had envelope in it. Secondly, it's a DNA prime followed by an adenovirus boost. The animal model showed clearly that it had an effect in both simian immunodeficiency virus (SIV) and SHIV (an SIV/HIV hybrid). It wasn't an overwhelming, knock-me-off-my-chair effect, but it clearly was quantitatively and qualitatively a bit better than the candidate tested in the STEP trial.

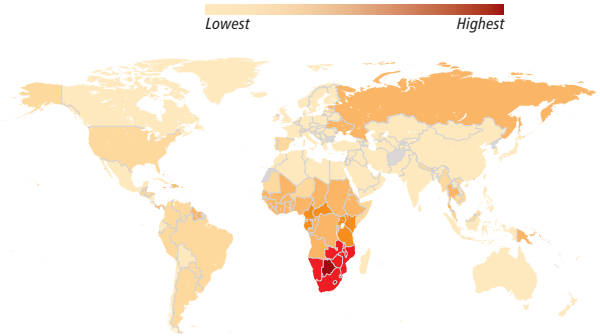
In looking at the data, I believed that there was enough difference to warrant a truncated, lean but mean, proof-of-concept trial. The first time, they came back with a trial that in my mind was still too large because it was powered to determine the correlates of immunity. I said, show me a trial that is powered to show if the candidates either work or don't work. If the candidate works, then we'll build on that trial.

April 2009
Nearly 28 years after the first five cases of AIDS are reported, the relentless search for a vaccine continues. Fauci is now serving his fifth president. His goal remains the same, even though he acknowledges that an AIDS vaccine may not, in fact, be possible.

Fauci: Don't be frightened but we may not ever have an AIDS vaccine in the classical sense of being 95% protective. Am I diminishing our efforts? No. In fact, I'm accelerating the vaccine research efforts, at least on the part of NIAID. Unlike other vaccine endeavors, we're still in the stage of discovery, and discovery is haphazard—sometimes blind alleys, sometimes Eureka moments—and completely unpredictable. We still don't know how, why, or if a body makes a robust neutralizing antibody and T-cell response that can both block acquisition and prevent disease progression. The reason we don't know this, is because the body doesn't do it in natural infection. With other viruses, nature tells us just follow me and I'll lead you to a vaccine. With HIV, nature is telling us if you follow me, you're going to be in trouble. We're going to have to push the envelope with HIV vaccinology in ways that we never had to do before. I feel that as we probe the scientific secrets of HIV, we may get there. If we can, with our own capabilities, intellect, and drive, manipulate the immune system to do something that natural infection doesn't seem to be able to do, what else can we do with the immune system? The vista is almost infinite.

A video podcast with Fauci can be viewed or downloaded at *www.iavireport.org*

HIV Prevalence Worldwide
(Adults, 2007)



Adults and Children Living with HIV (2007 estimates)

North America	1,200,000
Caribbean	230,000
South America	1,700,000
Europe	730,000
North Africa and Mideast	380,000
Sub-Saharan Africa	22,000,000
Northern Asia	1,500,000
Southern Asia	4,200,000
East Asia	740,000
Australia & Oceania	74,000
TOTAL	**33,000,000**

Source: The Joint United Nations Programme on HIV/AIDS (UNAIDS)