HIV's Leading Men

Robert Gallo, *74, is the director and co-founder of the Institute of Human Virology (IHV) at the University of Maryland and co-founder of Profectus Biosciences. Gallo was working as a virologist at the US National Cancer Institute when the first cases of AIDS were reported. In 1984, his team reported the isolation of a retrovirus that was later determined to be HIV. Recently, IHV was the recipient of a US$23.4 million grant from a consortium led by the Bill & Melinda Gates Foundation to fund preclinical development of an AIDS vaccine candidate that Gallo and colleagues developed and hope to test in clinical trials.*

Luc Montagnier, *78, is co-founder and current president of the United Nations Educational, Scientific and Cultural Organization (UNESCO) World Foundation of Aids Research and Prevention in Paris. Last year, he accepted a professorship at Shanghai Jiao Tong University. In 1983, Montagnier and his colleague Françoise Barré-Sinoussi were the first to report the isolation of a new retrovirus, later determined to be HIV, from a patient, a finding for which they received the 2008 Nobel Prize in Physiology or Medicine.*

Q: You've now lived through three decades of AIDS. What were those early days like?

Gallo: It was horrible, stressful, and I'll add a third adjective, scary. That time was unimaginable. You saw patients who you became friendly with and watched them die. There was nothing we could do for them. Then there were the crackpots saying that AIDS doesn't exist, or that we created it to kill people.

Q: How would you describe your role in the discovery of HIV?

Gallo: Between 1982 and 1985 there was a tremendous amount of papers published, done chiefly by my lab. We provided the idea in 1982 that a retrovirus might be the cause of AIDS, and our lab succeeded in growing T cells obtained from a man with AIDS that contained two viral forms. But there is no question that Luc Montagnier's group at the Pasteur Institute made the first report of HIV being isolated in a patient. There was never a controversy over who discovered the virus. The dispute arose later when we developed a blood test for HIV and the Pasteur Institute wanted a share of the royalties. Importantly, our report on an extensive number of HIV isolates, plus the blood test, was the evidence that HIV was the cause of AIDS. For these reasons, Luc and I agreed on co-discovery.

Q: Are you more hopeful now about HIV vaccine development than you were in 2008 when you compared the results of the STEP trial—which showed the vaccine candidate was not effective and may have even increased risk of HIV infection in some volunteers—to the Challenger space shuttle disaster?

Gallo: I wasn't pessimistic when I made that comment. I'm one of the most optimistic people in the field of AIDS vaccine science. I said that because I thought the STEP trial was a mistake from day one. From my viewpoint, this was not the kind of vaccine to go forward with. I don't think we should test a vaccine based solely on cell-mediated immunity. I'm not saying cellular immunity is unimportant and antibodies are the masters, but you better have some antibody-mediated protection.

Q: You're now actively engaged in AIDS vaccine research. What do you think it will take to make a preventive AIDS vaccine?

Gallo: I believe antibodies must be part of an effective preventive vaccine. I believe broadly neutralizing antibodies [that protect against many different HIV strains] are important. However, I don't think they are the only thing that is important. Neutralizing antibodies are just one way to skin a cat. I think non-neutralizing antibodies will likely have a role too. And I believe that a successful vaccine must come close to providing sterilizing immunity.

Q: So do you think the field is on the right track?

Gallo: I think so, but we need to follow the science. I am aghast at arguments that claim that monkeys don't predict how vaccine candidates will work in humans and that we should just go forward anyway with clinical trials. We need to be extremely cautious against using that philosophy. Monkeys aren't perfect but they are a good model. The alternative is that he or she who has the power simply and arbitrarily decides what vaccine goes forward.

Q: If non-neutralizing antibodies are important, what do you make of the results of the RV144 trial in Thailand, the first to show any efficacy?

Gallo: Since RV144 was the first trial to show efficacy, I would analyze it up and down. I don't believe the critics that said it didn't work and attacked the US Army [a collaborator in the trial] unfairly. The way Sanofi Pasteur designed the insert for its vaccine candidate was very interesting to me and my colleagues, because they relied on some of the same key structural characteristics that we were using in developing our vaccine candidate. When I saw data that the RV144 vaccine candidate had shown very high efficacy during the first year I was interested because that is exactly what we were seeing at IHV with our candidate vaccine in primate experiments. ■

Q: What are your earliest memories of the discovery of HIV?

Montagnier: I remember reading in the newspapers that there was a new disease, the gay disease. When we learned of the transmission by blood in transfused patients and hemophiliacs, the idea started that it could be caused by an infectious agent—a virus or a bacterium—and since it was transmitted also in filtered products for hemophiliacs it was more likely to be a virus. Since we had the technology to detect retroviruses and grow human T cells, we started to look for a retrovirus.

I used a lymph node biopsy of a gay man who had swollen lymph nodes and I cultured his T cells. Three weeks later my associate, Françoise Barré-Sinoussi, was able to detect some retrovirus activity in the culture. So I set up a group of about 10 people, and this group within months in 1983 could show that the virus was new and was the best candidate to be the cause of AIDS.

Q: What did you think when you first saw this result?

Montagnier: We had the virus but we didn't know whether it was just a passenger virus or the cause of AIDS. So at this time we were moderately excited. We had to look for a correlation with the disease. This was done during 1983 and 1984 when my colleagues showed that there were antibodies against this virus in many pre-AIDS patients, and in some AIDS patients as well. We could also isolate the same type of virus not only from gay men, but also from hemophiliacs and from African patients, indicating that this virus was probably the best candidate for being the cause of AIDS.

Q: What was the response to your first paper in 1983?

Montagnier: Well, it was mostly ignored. We called the virus LAV (lymphadenopathy-associated virus) because it was isolated not from a full-blown AIDS patient, but from a pre-AIDS patient. Then, after the publication we found the same type of virus in the blood of full-blown AIDS patients. I think the first time I could convince at least some of my colleagues in the US was at Cold Spring Harbor in September 1983, where I presented all the data indicating this was the right virus to be the cause of AIDS.

Q: Do you think it will be possible to develop a preventive HIV vaccine?

Montagnier: That's a sensitive question. I think it's important to first continue some basic research in order to detect all forms of the virus which are transmitted. My approach is to first try therapeutic vaccines, which could be more easily tested in clinical trials in a very short period of time. Clinical trials of preventive vaccines are expensive and questionable in terms of the results because you need to deal with a large population in order to obtain significant results. If a therapeutic vaccine works, then we can extrapolate it to a preventive vaccine.

Q: Regarding the Nobel Prize, when you got that call were you surprised?

Montagnier: I cannot say I was very surprised because every year some journalists called me in advance of the announcement to see if maybe this is the year for me to win the Nobel. I was in Africa at that time, in a meeting in Ivory Coast, and of course it was symbolic as AIDS is mostly in Africa and a disease of developing countries.

Q: What would you tell people who are entering the field? What is there to still learn about HIV, 30 years later?

Montagnier: There are still many things to find. It's not finished. Even though we know very well the molecular biology of this virus, we still know little about how it is transmitted, why antiretroviral treatment cannot get rid of it completely, why there is a reservoir of the virus despite treatment, and so on. There are still basic questions to answer, and at the same time we have to save the lives of patients and try to reduce the duration of treatment. I think this is key if we are to beat this disease in the 21st century. I hope I will see that during my life. ■

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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 25 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it. For more information, go to www.iavi.org.

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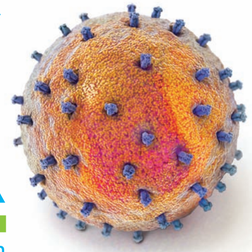
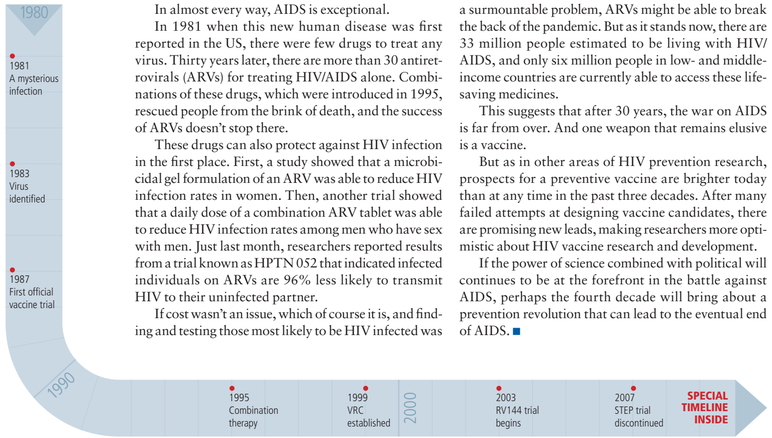
The Bulletin on AIDS Vaccine Research



30 years
of AIDS vaccine research



In almost every way, AIDS is exceptional.

In 1981 when this new human disease was first reported in the US, there were few drugs to treat any virus. Thirty years later, there are more than 30 antiretrovirals (ARVs) for treating HIV/AIDS alone. Combinations of these drugs, which were introduced in 1995, rescued people from the brink of death, and the success of ARVs doesn't stop there.

These drugs can also protect against HIV infection in the first place. First, a study showed that a microbicidal gel formulation of an ARV was able to reduce HIV infection rates in women. Then, another trial showed that a daily dose of a combination ARV tablet was able to reduce HIV infection rates among men who have sex with men. Just last month, researchers reported results from a trial known as HPTN 052 that indicated infected individuals on ARVs are 96% less likely to transmit HIV to their uninfected partner.

If cost wasn't an issue, which of course it is, and finding and testing those most likely to be HIV infected was a surmountable problem, ARVs might be able to break the back of the pandemic. But as it stands now, there are 33 million people estimated to be living with HIV/AIDS, and only six million people in low- and middle-income countries are currently able to access these life-saving medicines.

This suggests that after 30 years, the war on AIDS is far from over. And one weapon that remains elusive is a vaccine.

But as in other areas of HIV prevention research, prospects for a preventive vaccine are brighter today than at any time in the past three decades. After many failed attempts at designing vaccine candidates, there are promising new leads, making researchers more optimistic about HIV vaccine research and development.

If the power of science combined with political will continues to be at the forefront in the battle against AIDS, perhaps the fourth decade will bring about a prevention revolution that can lead to the eventual end of AIDS. ■

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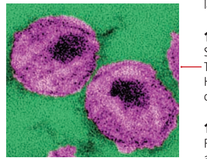
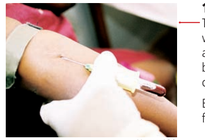
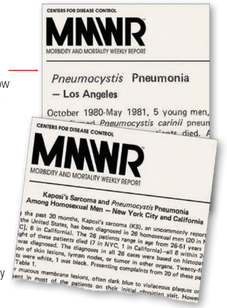
30 YEARS
OF AIDS VACCINE RESEARCH




Vanessa Vick

1981
In a chilling prologue to one of the worst pandemics in history, the US Centers for Disease Control issues a report on June 5 of an unusual spate of *pneumocystis carinii* pneumonia (an infection seen in severely immune-compromised individuals), among "five gay, otherwise healthy men." In July, 26 more cases are reported in California and New York. Those affected are now also developing Kaposi's sarcoma, a cancer caused by the herpes virus, which becomes a hallmark of this new disease.


CENTERS FOR DISEASE CONTROL
MMWR
MORBIDITY AND MORTALITY WEEKLY REPORT
Pneumocystis Pneumonia — Los Angeles
October 1980-May 1981, 5 young men, [illegible] *Pneumocystis carinii* pneum [illegible] died.
CENTERS FOR DISEASE CONTROL
MMWR
MORBIDITY AND MORTALITY WEEKLY REPORT
Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men — New York City and California
[illegible] the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported [illegible] the United States, has been diagnosed in 26 homosexual men [illegible] [C], 8 in California). The 26 patients range in age from 26 to 50 years. [illegible] light of these patients died (7 in NYC, 1 in California)—all 8 within 2 [illegible] were diagnosed. The diagnosis in all 26 cases were based on histopat [illegible] ion of skin lesions, lymph nodes, or tumor in other organs. Twenty-s [illegible] he were white, 1 was black. Presenting complaints from 20 of these pa [illegible] Table 1.
[illegible] mucous membrane lesions, often dark blue to violaceous plaques or [illegible] sent in most of the patients on their initial physician visit. Howev

1982
At a July 27 meeting in Washington, DC, the new disease is named acquired immunodeficiency syndrome (AIDS).

1983
US researchers publish the first report of eight infants who had a "disease complex comparable to AIDS."

French researchers from the Pasteur Institute isolate a new retrovirus from the lymphoid tissue of a gay Caucasian patient that may be the cause of AIDS. They later call the new virus lymphadenopathy-associated virus (LAV).

1984
Scientists in the US confirm the discovery of a new retrovirus, but call it human T lymphotropic virus (HTLV) type III. This discovery prompts US Health and Human Services Secretary Margaret Heckler to proclaim that an AIDS vaccine candidate would be ready for testing within two years.

1985
Researchers from Uganda report a new syndrome in 63 people that is strongly associated with HTLV-III. The researchers dub the condition Slim disease because it results in severe weight loss, and note that it seems to be occurring predominantly in the "heterosexually promiscuous population."


Vanessa Vick

1986
The International Committee on Taxonomy of Viruses rules that the new virus be called human immunodeficiency virus (HIV).

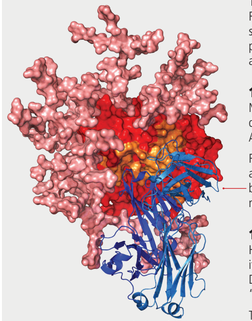
French researcher Daniel Zagury inoculates himself with a vaccine candidate containing a genetically engineered version of an HIV protein inside a viral vector based on the vaccinia virus (the same virus used in the smallpox vaccine). Zagury also vaccinates nine HIV-uninfected children from Zaire (now the Democratic Republic of the Congo), making this the first unofficial preventive AIDS vaccine trial. Researchers and ethicists criticize Zagury because the trial is conducted without French regulatory approval and without adequate preclinical testing.

1987
The first preventive AIDS vaccine trial in the US begins, involving 81 HIV-uninfected volunteers, mostly men who have sex with men (MSM). The study's collaborators are the National Institute of Allergy and Infectious Diseases (NIAID) and the biotechnology company MicroGeneSys, which developed the vaccine candidate containing a genetically engineered version of an HIV protein.

Efforts to protect chimpanzees from HIV using an experimental vaccine candidate fail. The candidate also used a vaccinia virus as a vector to deliver fragments of HIV.

1988
The UK Medical Research Council and the Uganda Virus Research Institute in Entebbe form Africa's first research unit focused on the determinants of HIV infection and disease progression.

1980s


Vaccine Research Center at NIAID

1992
Researchers report that rhesus macaques vaccinated with a live, attenuated simian immunodeficiency virus (SIV), the monkey equivalent of HIV, are protected against infection, raising hopes that this might be a feasible approach to HIV vaccine development.

1994
NIAID refuses to fund the first efficacy trial of an AIDS vaccine candidate that was developed by California-based biotechnology company Genentech. The candidate, AIDSVAX, contains a genetically engineered version of HIV's surface protein.

Researchers isolate a human antibody known as b12 from the bone marrow of an HIV-infected man who was asymptomatic for six years. In laboratory tests, b12 is able to neutralize more than 75% of HIV strains, making it a broadly neutralizing antibody (bNAb).

1995
Highly active antiretroviral therapy (HAART) is introduced. "From 1985 to 1994 it was all gloom and doom when it came to therapy," recalls AIDS researcher David Ho, who pioneered the use of a class of drugs called protease inhibitors. "Two years later, everything turned around."

The AIDS Vaccine Advocacy Coalition is formed on World AIDS Day.

1996
The International AIDS Vaccine Initiative (IAVI) is created as a non-profit, public-private product development partnership to ensure the development of a safe and effective preventive AIDS vaccine.

Researchers report that an attenuated SIV vaccine caused disease in infant macaques. These findings, along with other data in humans, dash hope that this would be a safe approach to test in humans.

1997
During a May 18 speech at Morgan State University in Baltimore, Maryland, US President Bill Clinton announces a national goal to develop an AIDS vaccine within a decade. Thereafter, that day is known as World AIDS Vaccine Day.

1998
VaxGen, a spinoff of Genentech, launches a Phase III efficacy trial of AIDSVAX, with the help of private investors. This is the first efficacy trial of an AIDS vaccine candidate. The trial enrolls 5,400 volunteers, mostly MSM, in the United States, Canada, the Netherlands, and Puerto Rico. A year later, another arm of the trial begins in Thailand, involving nearly 2,500 injection drug users.

1999
After a decade of planning, Africa's first AIDS vaccine trial starts in Uganda, testing ALVAC vCP205, a canarypox viral vector-based vaccine candidate (made by the French company Pasteur Mérieux Connaught, now Sanofi Pasteur), in 40 volunteers.

The Kenya AIDS Vaccine Initiative (KAVI) is established in collaboration with the University of Nairobi, Oxford University, and IAVI.

NIAID establishes the Vaccine Research Center (VRC) at NIAID, with a primary focus on AIDS vaccine development.

The HIV Vaccine Trials Network (HVTN), headquartered in Seattle, is formed by NIAID to test preventive AIDS vaccine candidates.

The South African AIDS Vaccine Initiative is formed by the government with the goal of coordinating and supporting the development of a safe and effective AIDS vaccine.


Andreas von Bubnoff

> **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.'
>
> —Anthony Fauci, NIAID Director


Jean-Marc Giboux/Getty Images

1990s

> **There are still basic questions** to answer, and at the same time we have to save the lives of patients and try to reduce the duration of treatment.
>
> I think this is key if we are to beat this disease in the 21st century.
>
> —Luc Montagnier

2003
Preliminary data from VaxGen's two Phase III trials show that AIDSVAX is not effective.

Twenty-four leading AIDS vaccine researchers publish a paper arguing that the scale of research is insufficient for solving the major scientific challenges impeding development of an AIDS vaccine. This leads to the creation of the Global HIV Vaccine Enterprise, an alliance committed to accelerating the development of an AIDS vaccine.

An efficacy trial known as RV144 begins in Thailand with funding from NIAID and the US Army. The trial, conducted by the Thailand Ministry of Public Health, tests a combination of two vaccine candidates (Sanofi Pasteur's canarypox vector-based vaccine candidate ALVAC-HIV vCP1521 and VaxGen's AIDSVAX) in 16,000 volunteers.


US Military HIV Research Program

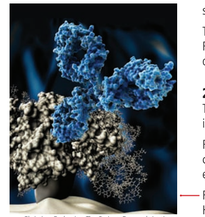
2004
Twenty-two prominent AIDS vaccine researchers publish an article questioning the scientific rationale for pursuing the RV144 trial, arguing that other candidates have a greater chance of success.

A Phase IIb test-of-concept trial known as STEP begins in North and South America, the Caribbean, and Australia. The 3,000-person trial tests the efficacy of Merck's MRKAd5 vaccine candidate in either preventing HIV infection or in reducing viral load among volunteers who become infected despite vaccination.

2005
NIAID announces US$300 million in funding over seven years to establish a virtual consortium known as the Center for HIV/AIDS Vaccine Immunology (CHAVI).

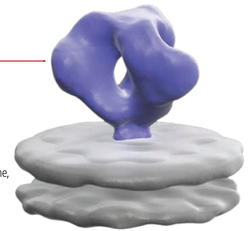
2006
The Bill & Melinda Gates Foundation awards $287 million to establish the Collaboration for AIDS Vaccine Discovery (CAVD) that supports 16 AIDS vaccine development centers.

2007
Vaccinations in the STEP trial are discontinued after a data safety monitoring board determines that the vaccine didn't work. Subsequent data shows that MRKAd5 may have increased the risk of HIV acquisition among a subset of volunteers. Vaccinations in the Phase IIb Phambili trial of the same vaccine candidate, which launched in South Africa in February, are also halted.


Christina Corbaci at The Scripps Research Institute

2008
Researchers obtain an improved 3D image of the structure of HIV's surface protein.

The Neutralizing Antibody Center, a partnership of IAVI and The Scripps Research Institute in California, where the center is based, is established to develop vaccine candidates that can elicit bNAbs.


Sriram Subramaniam, US National Institutes of Health

2009
The Ragon Institute, a research collaboration dedicated to finding an AIDS vaccine, is launched with a $100 million gift.

Results from the RV144 Phase IIb trial in Thailand show that the vaccine candidate reduces the risk of HIV infection by about 31%, providing the first evidence that a vaccine candidate can protect against HIV infection in humans.

For the first time in a decade, researchers isolate several new bNAbs against HIV from the blood of infected individuals.

2011
Results from analysis of immune responses in RV144 expected in September.

2000s