

40 years of AIDS vaccine research

There are many success stories over four decades of HIV/AIDS research.

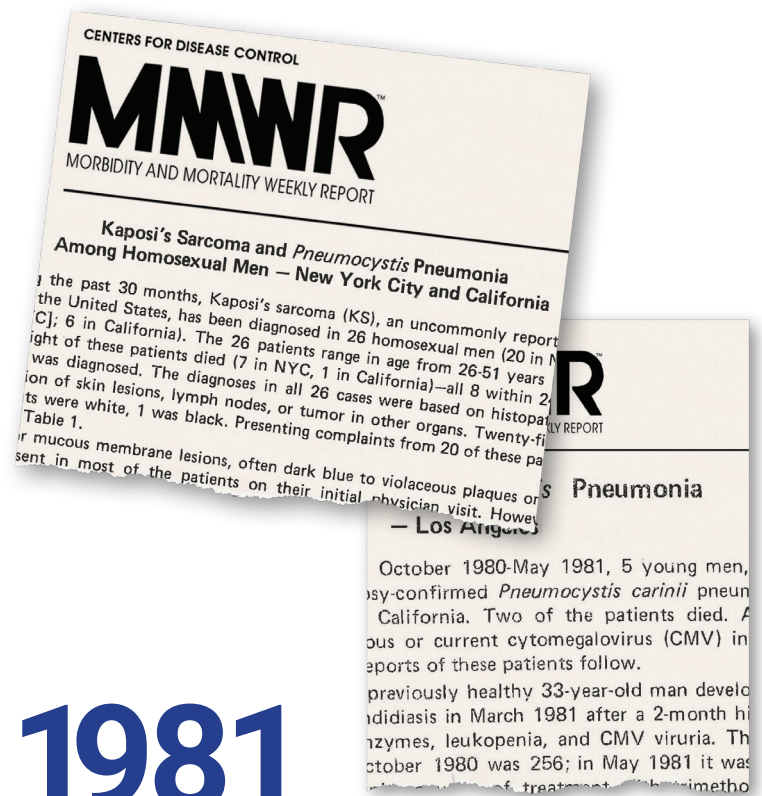
Life-saving antiretroviral therapy, introduced in 1995, is one of the most significant. Writing recently in *Nature*, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, recalls that in 1985, a 25-year-old diagnosed with AIDS in the U.S. had a life expectancy of fewer than two years. Whereas, today, a person living with HIV can expect instead to die in old age from causes unrelated to HIV/AIDS.

The heroic efforts of advocates and activists who pressured scientists, governments, and regulators to make these medicines more widely available were another important success story. Advances in HIV prevention science — including using antiretrovirals as pre-exposure prophylaxis — are yet another important success. Since its peak in 2004, AIDS-related deaths have plummeted by 64%.

Together, advances in HIV testing, treatment, and prevention have helped dramatically slow the spread of HIV. But they haven't stopped it. Last year, 1.5 million people were newly infected with HIV and 700,000 people died from AIDS-related illnesses.

A vaccine is one prevention tool that remains elusive. Research over the past 40 years, as evidenced by this timeline, illustrates just how difficult it is to induce effective immunity against this virus. But with each decade, scientists are making important progress. And, certainly, their persistence is commensurate with that of HIV.

The next decade will likely answer many questions about the feasibility of developing an HIV vaccine and will hopefully bring us closer to the ultimate end of this timeline — the end of AIDS.



1981

U.S. Centers for Disease Control issues a report on June 5 of an unusual spate of **pneumocystis carinii pneumonia**, among “five gay, otherwise healthy men.” In July, 26 more cases are reported. Those affected are now also developing Kaposi’s sarcoma, which becomes a hallmark of the new disease.

1982: New disease is named **acquired immunodeficiency syndrome (AIDS)** at a July 27 meeting in Washington, DC.

1980s

As scientists identify and begin grappling with the newly identified retrovirus that causes AIDS, vaccine researchers begin testing protein-based vaccine candidates in the first clinical trials.

> Basic science and clinical development

> Funding, collaborations, and advocacy

1983

- > Pasteur Institute researchers isolate **new retrovirus** from the lymphoid tissue of a gay Caucasian patient that may be the cause of AIDS. The virus is later called lymphadenopathy-associated virus (LAV).
- > First U.S. report of **eight infants** who had a “disease complex comparable to AIDS.” The children, who were born into families with “recognized risks of AIDS,” primarily intravenous drug use, had unexplained immune deficiencies and some of them had opportunistic infections that fit the description of AIDS.

1984

- > U.S. scientists confirm discovery of new retrovirus, calling it **human T lymphotropic virus** (HTLV) type III because they thought it was related to human T-cell leukemia virus (HTLV type I). This discovery prompts U.S. Health and Human Services Secretary Margaret Heckler to proclaim that an AIDS vaccine candidate would be ready for testing within two years.

1985

- > A new syndrome dubbed **Slim disease** is reported in Uganda that is strongly associated with HTLV-III.



- > Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases (NIAID), **quadruples funding** for AIDS research. The Division of AIDS is established within NIAID a year later.

1986

- > International Committee on Taxonomy of Viruses rules that this new virus be called **human immunodeficiency virus** (HIV).
- > After attempting therapeutic vaccination in two HIV-infected women from Zaire (now the Democratic Republic of the Congo), French researcher Daniel Zagury **inoculates himself** and nine HIV-uninfected children in Zaire with a vaccinia viral vector-based candidate, making this the first unofficial preventive AIDS vaccine trial. Zagury is criticized because trial is conducted without regulatory approval or preclinical testing.

1987

- > A recombinant vaccinia virus **vector-based vaccine fails** to protect chimpanzees from HIV.
- > First preventive AIDS **vaccine trial begins** in U.S. NIAID and the biotech MicroGeneSys test the company's recombinant gp160 vaccine candidate in 81 HIV-uninfected volunteers, mostly men who have sex with men (MSM).



1988


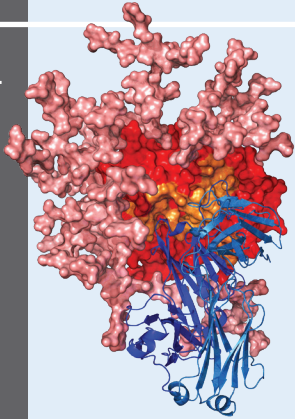
- > U.K. Medical Research Council and Uganda Virus Research Institute in Entebbe form **Africa's first research unit** focused on determinants of HIV infection.

1990s

Advances in treating HIV/AIDS dramatically alter the landscape of the disease in wealthy countries. Vaccine research begins in earnest with the start of the first Phase III efficacy trial and the creation of multiple initiatives focused on AIDS vaccine development.

> Basic science and clinical development

> Funding, collaborations, and advocacy

1992	<p>> Rhesus macaques vaccinated with a live, attenuated simian immunodeficiency virus (SIV), are protected.</p>	
1994	<p>> Researchers make a recombinant form of a human antibody called b12 from the bone marrow of an asymptomatic HIV-infected man. It neutralizes more than 75% of HIV strains, making it the first broadly neutralizing antibody (bnAb).</p> 	<p>> NIAID refuses to fund the first efficacy trial of an AIDS vaccine candidate developed by California-based biotech Genentech. The bivalent vaccine candidate, AIDSVAX B/B, is comprised of recombinant gp120 protein.</p>
1995	<p>> 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 protease inhibitors. "Two years later, everything turned around."</p>	<p>> The AIDS Vaccine Advocacy Coalition is formed on December 1, World AIDS Day.</p>
1996	<p>> The attenuated strain of SIV previously shown to protect monkeys against SIV infection leads to disease when used to vaccinate infant macaques, dashing hopes for testing this approach in humans.</p>	<p>> 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.</p>
1997	<p>> At a May 18 speech, U.S. President Bill Clinton announces national goal to develop an AIDS vaccine within a decade. The day is then known as World AIDS Vaccine Day.</p>	

1998	<ul style="list-style-type: none"> > Genentech spinoff VaxGen launches Phase III efficacy trial of AIDSVAX B/B, enrolling 5,400 volunteers, mostly MSM, in the U.S., Canada, the Netherlands, and Puerto Rico. A year later, another Phase III trial of AIDSVAX B/E candidate starts in Thailand in a trial of 2,500 injection drug users. 		
1999	<ul style="list-style-type: none"> > The Vaccine Research Center (VRC) is established on the NIH campus to perform basic research to establish mechanisms of inducing long-lasting, protective immunity against HIV and other pathogens. 	<ul style="list-style-type: none"> > Uganda hosts Africa's first HIV vaccine trial. 	<ul style="list-style-type: none"> > The Kenya AIDS Vaccine Initiative (KAVI) and South African AIDS Vaccine Initiative are established. > The HIV Vaccine Trials Network (HVTN) is formed by NIAID.

2000s

Disappointing results from the largest vaccine trial to date testing a candidate that induces T-cell immunity are followed by a surprising result from the RV144 trial – the first to show any evidence that a vaccine can protect against HIV. Meanwhile, key discoveries related to broadly neutralizing antibodies jump-start a new pathway to HIV vaccine development.

> **Basic science and clinical development**

> **Funding, collaborations, and advocacy**

2002	<ul style="list-style-type: none"> > NIAID assumes control of the U.S. Department of Defense's HIV Research and Development Program, which had been preparing to launch a Phase III efficacy trial, RV144, in Thailand testing Sanofi-Pasteur's canarypox vector-based vaccine candidate ALVAC-HIV (vCP1521) in a prime-boost combination with VaxGen's AIDSVAX B/E candidate. 	
2003	<ul style="list-style-type: none"> > Phase III trials show that AIDSVAX is ineffective in either MSMs or IDUs. > RV144 prime-boost trial begins in Thailand in 16,000 mostly low-risk volunteers. 	<ul style="list-style-type: none"> > Twenty-four leading AIDS vaccine researchers publish a paper arguing that the insufficient scale of research is impeding development of an AIDS vaccine. Several years later, the Global HIV Vaccine Enterprise is created.
2004	<ul style="list-style-type: none"> > 22 prominent researchers publish an article questioning scientific rationale for RV144 trial. 	<ul style="list-style-type: none"> > Start of the Phase IIb STEP trial testing whether Merck's adenovirus serotype 5 (Ad5) candidate can either prevent infection or reduce viral load.
2005	<ul style="list-style-type: none"> > NIAID announces US\$300 million over seven years for virtual consortium, the Center for HIV/AIDS Vaccine Immunology (CHAVI). 	

2006

- > Researchers in Kenya isolate a subtype A transmitted/founder virus from a six-week-old infant in Nairobi who was HIV infected at birth and enrolled in a mother-to-infant HIV transmission study. This virus sequence is referred to as **BG505**.
- > With support from USAID, IAVI initiates large multi-center epidemiology studies. One of them, **Protocol G**, aims to identify new HIV-specific bnAbs to inform vaccine design efforts.

Read
the study



- > The Bill & Melinda Gates Foundation awards \$287 million to establish the **Collaboration for AIDS Vaccine Discovery (CAVD)**.

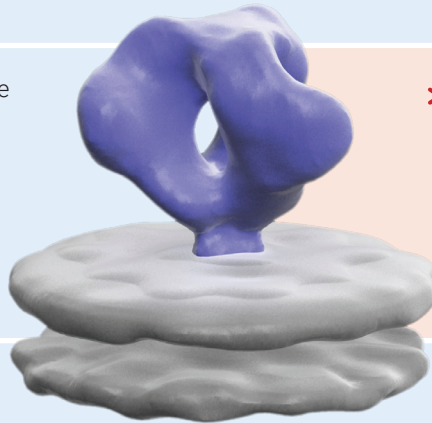
2007

- > Vaccinations in STEP are discontinued because there is **no evidence of protection**. Subsequent data suggest that vaccine candidate MRKAd5 may have increased risk of HIV among some volunteers. Vaccinations in Phase IIb Phambili trial of same candidate, which launched in South Africa in February, are also halted.

- > STEP results prompt NIAID to **reconfigure** Phase IIb PAVE 100 trial of a DNA/Ad5 prime-boost regimen.

2008

- > A hi-res, 3-D image approximates the **trimeric structure** of HIV gp120.



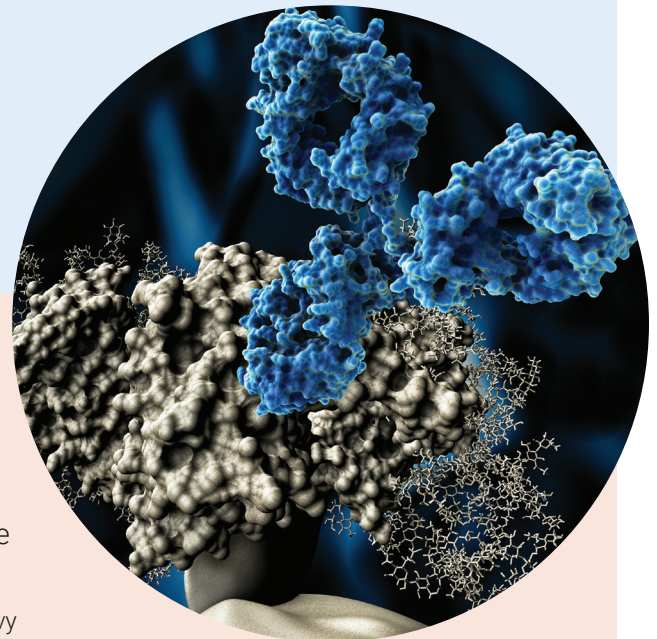
- > Following STEP results, NIAID sponsors summit about **shifting funding** from clinical development to basic discovery.

- > The **Neutralizing Antibody Center**, a partnership of IAVI and The Scripps Research Institute in California, is established.

2009

- > RV144 results show vaccine candidate reduces risk of HIV infection by about 31%, providing **first evidence** of vaccine efficacy in humans.

- > **New bnAbs** isolated that are more broad and potent, and that target new epitopes on HIV.




- > **The Ragon Institute** launches with a \$100 million gift, joining researchers from three Boston institutions.

- > The AIDS Vaccine Conference draws a record number of attendees as the field seems **more optimistic** about the prospects for HIV vaccine development.

“
We are at the beginning of a new phase of HIV vaccine research.

—Yves Levy

”

 [Read the 2009 story](#)

2010s

Researchers are exploring multiple paths to HIV vaccine development. One path is to design and test mosaic vaccine antigens that are meant to address HIV's overwhelming global diversity. Another is to explore the role of non-neutralizing antibodies in the role of HIV protection. At the same time, researchers hone in on HIV's elusive structure and use this information to design vaccine candidates to induce broadly neutralizing antibodies.

> **Basic science and clinical development**

> **Funding, collaborations, and advocacy**

2010

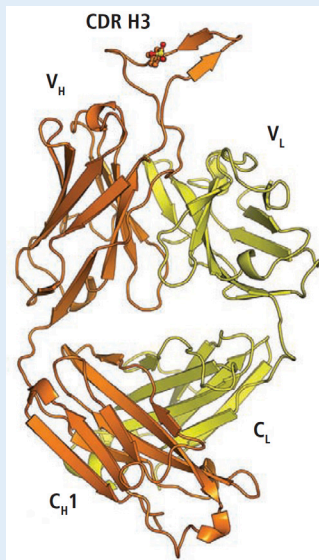
- > **Mosaic antigens**, computationally derived to provide maximum coverage against HIV, show promise in monkeys.
- > Researchers analyze the structure of recently identified bnAbs to determine how they bind to and neutralize HIV. This work shows the extensive **affinity maturation** that gives rise to these antibodies, which has consequences for vaccine design.

- > Researchers show that **cell-to-cell spread** of HIV *in vitro* is about 10 times more efficient than infection spread by free-virus particles.

 [Read the study](#)

- > In the wake of the RV144 results, researchers home in on the role **non-neutralizing antibodies** may play in protection against HIV.

- > Researchers identify crystal **structure of PG16**, one of the recently identified bnAbs, revealing its unique features.




- > The **Pox-Protein Public-Private Partnership** (P5) collaboration is established to explore and expand on the results of the RV144 trial – the only vaccine candidate to show any efficacy in preventing HIV infection.
- > *IAVI Report* profiles Bette Korber of the Los Alamos National Laboratory on **HIV evolution** and diversity.

“

We have to deal with the diversity issue. If we don't, we will never have a vaccine that works.

—Bette Korber

”

 [Read the 2010 story](#)

2011

- > Researchers continue **isolating dozens** of new broadly neutralizing antibodies and gather clues about how they develop in infected individuals.

- > Vaccination with a **replication competent CMV** vector-based vaccine leads to viral control in SIV-challenged monkeys.

 [Read the study](#)

- > **HVTN 505 vaccine trial** is expanded to explore whether the DNA/Ad5 prime-boost regimen can block HIV infection.

2011

> Researchers from Emory and Beth Israel Deaconess Medical Center are selected to lead a 5-year, \$60 million effort to use **NHP models** to understand mucosal HIV transmission.

> Researchers debate how **adaptive clinical trial designs** could speed the evaluation of vaccine candidates.

> IAVI Report interviews **four leading researchers** on what it will take to go from broadly neutralizing antibodies to vaccine immunogens.

Read the story 

“

I think this is a tipping point in a way. The next two, three, four years will tell us a lot about the feasibility of an HIV vaccine.

—Dennis Burton

”

2012

> Additional analyses of RV144 results provide some insight into what types of **immune responses** may have contributed to protection.

 Read the study

> The U.S. NIAID announces two consortia known as the **Center for HIV/AIDS Vaccine Immunology & Immunogen Discovery** (CHAVI-ID) to tackle scientific obstacles to HIV vaccine development. The two centers were established at Duke University and The Scripps Research Institute (TSRI) in La Jolla, CA.

> **IAVI-Translational Health Science and Technology Institute** (THSTI) HIV Vaccine Translational Research Laboratory opens in India to study genetic and virological properties of circulating HIV strains in India.

2013


> Scientists at TSRI and IAVI apply computational and genetic engineering techniques to generate a virus-like particle (eOD-GT6) that **activates bnAb precursors** in the lab — an initial step in developing a vaccine immunogen capable of setting off the development of bnAbs.

> Using BG505 SOSIP.664, researchers capture cryoelectron microscopy and x-ray crystallography images of a **native-like HIV Env trimer**.

 Read the study

> The Bill & Melinda Gates Foundation awards a grant to IAVI to create the **Vaccine Product Development Center** (VxPDC) to assist investigators affiliated with the Foundation's Collaboration for AIDS Vaccine Discovery with the complex process of transitioning vaccine candidates from the laboratory to the clinic.

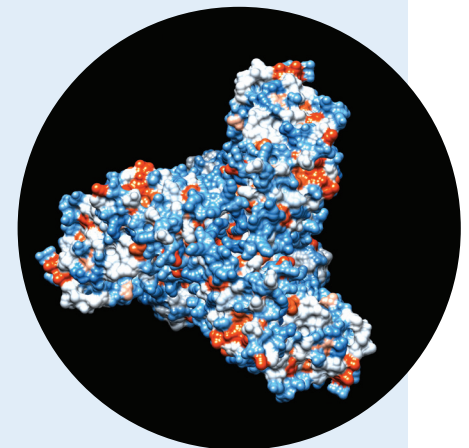
> IAVI expands the Product Development Center (PDC) to **support other products** in addition to vaccines and extends its translational expertise to other partners.

 Learn more about the PDC

> The **Human Vaccines Project** launches to accelerate the development of new vaccines by decoding the human immune system.

> Researchers publish data on a **stabilized HIV trimer protein** known as BG505 SOSIP.664 based on an isolate from an HIV Clade A-infected infant in Kenya.

 Read the study



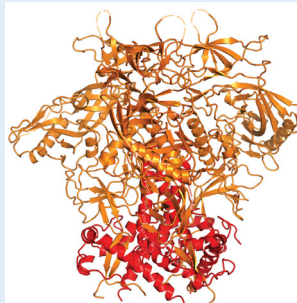
2013

> Immunizations in the Phase IIb HVTN 505 trial are stopped prematurely because the DNA/Ad5 prime-boost vaccine regimen **was not effective** at either preventing HIV infection or lowering viral load in individuals who acquired HIV despite vaccination.

[Read the study](#)

> Researchers at the VRC announce plans to begin a **passive immunization** clinical trial with the VRC01 bnAb.

> Two studies published in *Science* describe the **structure of the notoriously unstable HIV trimer**, a long-term goal of HIV vaccine researchers. This helps accelerate structure-based vaccine design efforts.



“
It’s really the start of a new generation of immunogens and vaccines that weren’t previously accessible.
”

—Andrew Ward

2014

> Researchers report on the **identification of bnAbs** from a South African donor, CAP256, which have increased breadth and potency.

[Read the study](#)

> The bnAb **PIGDM1400** is identified and is among the most broad and potent antibodies isolated to date.

[Read the study](#)



> With support from USAID through PEPFAR, IAVI launches **Vaccine Immunology Science and Technology for Africa** (VISTA) and the International Training Program to strengthen research capacity for HIV vaccine research in sub-Saharan Africa.

2015

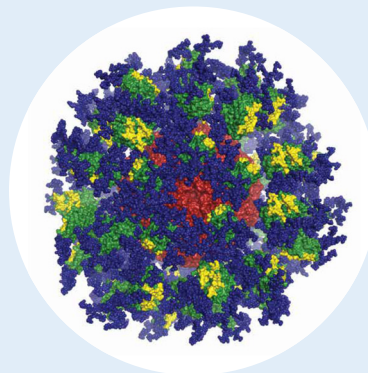
> Researchers **make progress** in developing native-like HIV Env trimers as vaccine immunogens.

2016

> Studies in transgenic mice show that the engineered eOD-GT8 60mer immunogen followed by a native like trimer immunogen **can induce VRC-01-like antibodies**.

[Read the study](#)

> The **AMP studies** are launched to test whether intravenous infusions of the bnAb VRC01 is effective at preventing HIV infection.



> The Phase IIb/III HVTN 702 trial, known as **Uhambo**, is launched to test whether a modified version of the vaccine candidate tested in RV144 is effective at preventing HIV infection in South Africa.

[Learn more](#)

2017

> Researchers generate a **trisppecific HIV bnAb** that can protect against a modified simian/human immunodeficiency virus in macaques.

> Researchers at the VRC isolate the N6 bnAb that can **neutralize 98% of HIV isolates**.

[Read the study](#)

2017

- > The Imbokodo or HVTN 705/HPX2008 Phase IIb trial begins in South Africa. It is designed to test the efficacy of an **Ad26-vector-based HIV vaccine candidate** that delivers mosaic antigens designed to induce immune responses against a wide variety of global HIV strains.

“

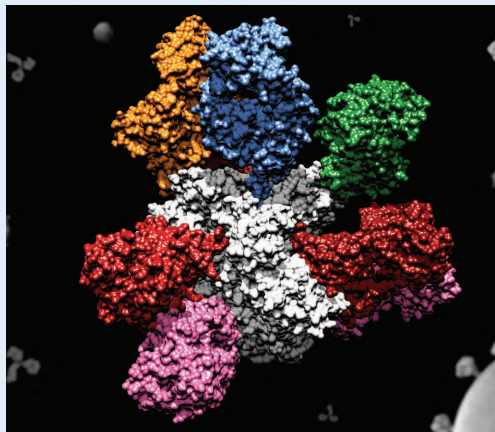
At a certain point you have to jump and hope that it works.

—Paul Stoffels, chief scientific officer at Johnson & Johnson

”

2018

- > The European AIDS Initiative 2020 program works to advance several **native-like HIV Env trimer immunogens** into clinical trials.
- > IAVI begins the first clinical trial of the eOD-GT8 60mer vaccine immunogen, which is designed to stimulate the immune system to initiate a **key first step** in the generation of bnAbs.



“

“It’s a new era clinically of testing this antibody-based vaccine design concept.”

—John Mascola

”

- > Several trials testing **passive administration** of HIV broadly neutralizing antibodies are underway by the VRC and researchers at Rockefeller University.

- > IAVI **expands its focus** to include developing vaccines against emerging infectious diseases, including Lassa fever and TB.



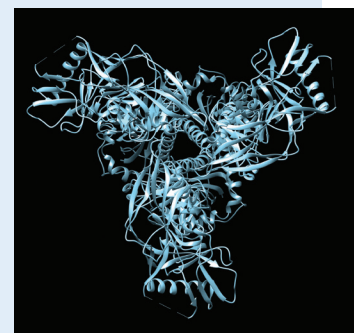
- > IAVI and the Serum Institute of India partner to develop and manufacture **globally affordable and accessible** antibody products for HIV.



2019

- > The European Union approves an **Ebola vaccine** that utilizes a vesicular stomatitis virus vector, which is also being explored for HIV vaccines.
 - > The **Mosaico** or HVTN 706/HPX3002 Phase III trial begins in North and South America and Europe testing the efficacy of an Ad26-based mosaic HIV vaccine candidate in men who have sex with men and transgender people.

- > IAVI starts a **Phase I clinical trial** (IAVI W001) of a native-like HIV envelope vaccine candidate (BG505 SOSIP.664 gp140) in Nairobi, Seattle, and Boston.



- > The **Duke Consortia for HIV/AIDS Vaccine Development** (CHAVD) receives a third seven-year grant from NIAID to develop and test vaccine candidates.

- > *IAVI Report* publishes a special issue on **African-led HIV vaccine science**.



2020s


More disappointing results from clinical trials are reported, causing many in the field to coalesce around the idea that an effective HIV vaccine will need to induce broadly neutralizing antibodies against the virus. In pursuit of that goal, researchers push ahead with structure-based immunogen design efforts.

> Basic science and clinical development

> Funding, collaborations, and advocacy

2020

- > Vaccinations in the Phase IIb/III HVTN 702 or Uhambo trial are **stopped early** because the vaccine candidate did not provide protection.

 [Learn more](#)

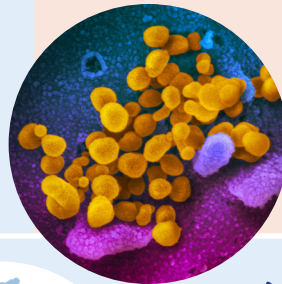
- > The **PrEPVacc trial begins** enrollment. This African-led Phase IIb/III clinical trial is evaluating two experimental HIV vaccine regimens compared to placebo, as well as a new PrEP combination pill known as Descovy. This is the first time that oral PrEP and experimental vaccines are being tested at the same time.

- > IAVI, Scripps Research, and the NIH agree to **pool their HIV bnAb assets** and expertise to develop a combination bnAb product specifically designed to be available and affordable globally.

[Learn more](#)



- > Decades of research on HIV facilitates the rapid development of vaccines against SARS-CoV-2, a **novel coronavirus** that spreads globally and kills millions.



2021


- > Following the results of the **Uhambo trial**, more and more researchers in the field converge on the idea that an effective vaccine will need to induce so-called bnAbs.




- > Results of the **Antibody Mediated Prevention trials** show that the antibody VRC01 did not protect against HIV infection any better than placebo.

- > Vaccinations begin in Zambia for a Phase I trial testing a **mosaic HIV vaccine** candidate known as HIVconsvX.

- > IAVI and Scripps Research announce that an experimental HIV vaccine candidate (eOD-GT8 60mer) **primed the immune system** as the first stage in the production of bnAbs in a Phase I clinical trial (IAVI G001).

 [Learn more](#)

- > Data from the Phase IIb **Imbokodo trial** show that the mosaic-based HIV vaccine regimen did not provide sufficient protection against HIV infection.

 [Learn more](#)

- > **IAVI Report** surveys leading researchers, funders, and policymakers on what the **AMP results** mean for the field.

[Read the story](#)



- > **IAVI commemorates 25 years** of translating scientific discoveries into affordable, globally accessible public health solutions.

[Learn the history](#)



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