

History of Vaccines



THE FUTURE OF IMMUNIZATION

The Development of HIV Vaccines

 English

At a time when many infectious diseases were being brought or kept under control with global vaccination efforts in the 1990s, the human immunodeficiency virus (HIV), only identified in 1984, infected millions worldwide. From 1990 to 2014 the number of people living with HIV rose from 8 million to 36.9 million; since the beginning of the HIV/Acquired Immune Deficiency Syndrome (AIDS) epidemic, AIDS has claimed more than 34 million lives.^[1]

HIV is a major public health concern not only because it can't yet be prevented by vaccination, but also because those it infects are infected for life with a virus that targets their immune system - making them more prone to *other* infections. The virus kills immune T helper cells called CD4+ cells, which are the coordinators of the human immune system. This is where the "Acquired Immune Deficiency Syndrome" name comes from: when HIV kills enough CD4+ cells, the infected person's immune system is unable to fight off infections it could ordinarily control. When the number of CD4+ cells drops below a certain point, a person is considered to have progressed from HIV infection to AIDS. People with AIDS are more susceptible to many types of infections, including those it could normally fight off, including types of pneumonia, tuberculosis, and shingles, as well as certain cancers.^[2]

In the early years of the AIDS epidemic, people infected with the virus faced certain death, often within just a few years after infection. Though many in the medical and public health fields lobbied to direct funding and research efforts to the growing crisis, U.S. government response was very slow. Factors that led the U.S. government to take action included vocal activism by people infected with HIV and their allies as well as persistent efforts by advocates in the scientific world. They highlighted the need for effective treatments, the need to improve access

to effective treatments once they were developed, and the importance of reducing the stigma of living with HIV infection.

While antiretroviral treatments have drastically improved life expectancy and quality of life for people living with HIV, preventing HIV infection is still a primary goal, especially for developing countries that are hardest hit by the pandemic and cannot afford treatments. Decades of effort have been spent, and continue to be made, toward developing an HIV vaccine.

This particular virus, however, poses unique challenges to vaccine development.

In general terms, all vaccines work the same way: they prime the immune system to recognize and attack a particular pathogen if it shows up in the body in the future. This can be done in a variety of ways: you can generate a vaccine by inactivating the pathogen (as in the injected polio vaccine) or weakening it (as in the measles vaccine), by using only part of it (pertussis), or by combining it with something else that helps it provoke an immune response (pneumococcal vaccine). Whichever method is used, the vaccine primes the immune system to respond quickly to the pathogen if it enters the body in the future.

HIV's Unique Challenges

In April 1984, U.S. Health and Human Services Secretary Margaret Heckler made a hopeful statement about an HIV vaccine, based on a conversation she'd had with the virus's co-discoverer, Robert Gallo: she said in a press conference that "We hope to have a vaccine ready for testing in about two years."^[3] Certainly, this prediction was overly optimistic, given that most vaccines take 10-20 years to develop. But 30 years later, why is there no licensed HIV vaccine?

In short, reasons generally given are

- Lack of natural immunity to HIV
- Variability of HIV types
- Lack of correlates of protective immunity
- Lack of an animal model that reliably predicts vaccine efficacy in humans

All of these factors make it difficult to select and prioritize vaccine candidates for further development. They are explained below.

HIV challenges the standard vaccine approaches first and foremost because, unlike diseases such as measles and chickenpox, no one naturally recovers from infection with HIV. If a person is infected with measles and survives, the immune response to the infection will usually be sufficient to prevent future infection with the measles. Researchers can use this naturally derived immunity as a model for the level of protection a successful vaccine should provide.

Without a model for natural immunity, researchers do not have a way to identify an immune response that would be effective against HIV, and thus developing an HIV vaccine is much more difficult. (Some individuals are naturally able to control the infection and prevent it from progressing to AIDS. Research into how these individuals, referred to as “elite controllers,” are able to control the infection offers another possible avenue toward vaccine development.)

A second challenge in developing a vaccine is that HIV mutates frequently. These frequent changes in the virus make it a difficult moving target for a vaccine. Additionally, there are many subtypes of HIV, each of which is genetically distinct; it’s likely that additional subtypes will continue to emerge. This poses yet another challenge, as a vaccine that protects against one subtype may not provide protection against others.

A third challenge (related to the first) is that researchers have not been able to determine what is known as the correlate of protective immunity to HIV infection. A correlate of protective immunity is defined as “a specific immune response that is closely related to protection against infection, disease, or other defined end point.” Because no one is known to have been infected with HIV and then naturally cleared the virus*, we do not know what protection from HIV would look like in a person. Would it be production of a certain kind and number of antibodies? Would it be the persistence of a certain kind of memory T cell? Until researchers have established what the correlates of protective immunity to HIV infection are, designing and validating a vaccine will be difficult.

Finally, animal models are an important tool in understanding the basic pathway of infection and immune system response in most diseases as well as in vaccine research. However, there is no reliable, non-human animal model for HIV infection and immune system response. HIV vaccine tests in animals have not yet yielded accurate predictions of how the vaccines will work in humans. Researchers continue to perform trials testing vaccines against Simian Immunodeficiency Virus (SIV), the monkey virus related to HIV, and against genetically engineered hybrids of SIV and HIV in hopes of using similar approaches against HIV.

Recent Cause for Optimism

In 2009, the results of the largest HIV vaccine trial in history were announced. Referred to as “RV144” or “the Thai trial” (as it took place in Thailand), it had more than 16,000 participants and took six years to complete.

The trial used a “prime-boost” strategy with two experimental HIV vaccines. The first was a recombinant vaccine using a canarypox virus, with inserted genes that code for antigenic proteins from HIV.^{[4][5]} This vaccine was used as the “prime” and was intended to stimulate cell-mediated immunity (T cell responses). The “boost” vaccine was composed of a genetically engineered antigenic surface protein from HIV, and was intended to stimulate antibody production (that is, B cell responses).^{[6][7]}

The prime vaccine had never been tested for efficacy against HIV in humans (although it had been through numerous safety trials). The boost vaccine had previously failed to show efficacy against HIV when tested. But when they were used in combination in the RV144 trial, the vaccines were moderately effective in preventing HIV infection. Specifically, there were 31% fewer HIV infections in trial participants who got the prime-boost combination than among those who got a placebo.

A 31% level of efficacy is not high enough to warrant use of a vaccine outside a trial setting, especially for a disease as serious as HIV. Yet this was the first time an HIV vaccine efficacy trial actually showed evidence of protection against the virus, giving researchers hope that an effective HIV vaccine is possible.

Current Status of HIV Vaccine Development

The first priority in light of the positive results from the RV144 trial is for researchers to determine the correlate of protection from the prime-boost vaccine combination: that is, they must determine precisely *how* the prime-boost combination protected against infection with HIV. Researchers have studied the antibodies induced by the prime-boost combination (which include multiple types of antibody responses); whether T-cell responses occurred; and whether the individual genetics of the study’s participants played a role in their responses to the vaccine combination. A study published in 2012 indicates that T-cell responses likely did not play a role in protecting against infection, and that the vaccine’s efficacy was related to antibody responses to certain regions of viral envelope proteins.^[8]

Additional studies are ongoing to try to understand and improve upon the immune response generated in the RV144 trial. The **P5 Partnership** (Pox-Protein Public-Private Partnership) has planned sequential future efficacy studies of RV144.

Researchers are also studying the methodology and administrative approaches of RV144, in hopes of applying the knowledge gleaned from the largest HIV vaccine trial in history to improve the design of future trials. The trial was a major international collaboration between non-profit groups, private companies, and the Thai and U.S. governments: the two vaccines had originally been developed by VaxGen and Sanofi Pasteur; trial funding was provided by the U.S. National Institutes of Allergy and Infectious Diseases and the U.S. Army Medical Research and Materiel Command; and the study's execution was carried out through the efforts of numerous cooperating organizations, led by the Thai Ministry of Public Health. Vaccine developers think that much can be learned by examining not just the outcomes of the RV144 trial, but the challenges that arose over its six years and how the participating organizations handled those challenges.

Efforts and approaches completely separate from the RV144 trial are underway. Researchers are studying the previously mentioned "elite controllers" whose HIV infections never progress to AIDS, in hopes that whatever innate ability they have to control HIV might provide insights for vaccine development. Efforts are also being made to study individuals who never become infected with HIV despite being exposed to it repeatedly.

Many other vaccine candidates are in various stages of testing and development. In addition to the canarypox-based recombinant vaccine used as the "prime" in the RV144 trial, recombinant candidates have also been developed based on adenovirus. A recent trial of this vaccine approach (HVTN 505) was halted in July 2013 because the vaccine failed to lower risk of infection in the recipients.^[9] Other genetically engineered candidates consist of a protein administered with an adjuvant – an agent included to further stimulate the immune system.

Additionally, the positive results of a SIV vaccine trial in rhesus macaque monkeys have raised the idea of using cytomegalovirus (CMV) as a vector in future HIV vaccine candidates. In this approach, T cells known as killer T cells, which can kill infected cells, provide the protection afforded by the vaccine.^{**[10]}

Other vaccine approaches are advancing, such as candidates that stimulate immune responses in the mucosal surfaces of the gut – the same site of early HIV replication.

Finally, researchers are exploring ways of generating antibodies to HIV. Antibodies are able to neutralize viruses before they infect a person. The results of collaborative work in the last two years shows that some humans produce antibodies capable of neutralizing a wide range of HIV strains. These antibodies provide an excellent target for vaccine discovery by highlighting weaknesses on the surface of HIV.

Therapeutic Vaccines

The HIV vaccines discussed above are intended to be preventive vaccines. That is, they are designed to prevent HIV from infecting the body. A therapeutic vaccine is a different kind of vaccine design, one that would be used after infection already has occurred. Most researchers think that a therapeutic HIV vaccine would not be a cure – that is, it probably would not rid the body of virus and lead to stopping anti-retroviral therapy. However, such a vaccine could boost the body's immune response to the virus, thus reducing the amount of virus in the body, reducing the risk of serious disease, and possibly reducing the dose of antiretroviral drugs needed. Several such therapeutic vaccines are undergoing clinical trials.^{[11][12]} In July 2014, results from the first phase of a small 2014 study of the drug romidepsin in combination with a vaccine candidate were announced at the International AIDS Conference in Melbourne. HIV-infected individuals received the vaccine to establish the basis for a memory immune response. Then the subjects received the drug, which was given with the goal of coaxing HIV out of hidden reservoirs in the body. Results of phase 1 of the trial were positive: the drug "kicked" HIV out of reservoirs and increased detectable quantities of HIV. The next phase of the trial, which should demonstrate whether the vaccine is effective at disabling HIV-infected cells, is expected to be completed in 2015.^{[13][14]}

Looking Forward

Many different groups are collaborating on these and other approaches to HIV vaccine development – perhaps more than for any vaccine development effort to date. Non-profit organizations, governments, pharmaceutical companies, philanthropic groups, and advocacy organizations are working together in what has become a truly global effort toward an HIV vaccine.

** *The only other SIV vaccine to generate longer-lasting immunity than the CMV-based vector vaccine was one containing live, attenuated Simian Immunodeficiency Virus. This approach is not considered to be a possibility for humans, as a live HIV vaccine, even weakened, would be too dangerous for human testing.*

Current Trials

The International AIDS Vaccine Initiative maintains a list of current and past AIDS vaccine trials, sorted by status, trial phase, and strategy. See the database here: **IAVI Trials Database**

Further Reading

You can keep up to date with the latest news about HIV vaccine research via the following organizations:

- International AIDS Vaccine Initiative (**iavi.org**)
- U.S. Military HIV Vaccine Research Program (**USMHRP**)
- HIV Vaccine Trials Network (**HVTN**)

Sources

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