

Developing a vaccine against HIV infection



KEY POINTS

- Researchers have been working on an HIV vaccine since the 1980s, but progress towards an effective vaccine has been much slower than anticipated.
- Finding at least a partially effective vaccine remains of critical importance for the HIV response.
- The biggest reduction in new infections would be achieved by a combination of PrEP, universal antiretroviral treatment for people already living with HIV, and a vaccine.¹
- An HIV vaccine is a more realistic prospect today than a decade ago and an optimistic forecast of HIV vaccine availability is that one might be available by 2030.

Explore this page to find out more about [the need for a vaccine against HIV](#), [challenges in vaccine development](#), [progress in developing a vaccine](#) and [achieving an effective vaccine for HIV](#).

What is an HIV vaccine?

Today, an effective vaccine against HIV does not exist. A vaccine that can prevent infection would teach the immune system to respond to HIV by making antibodies that can bind to the virus and stop it from infecting cells, or by promoting other immune responses that kill the virus.

No vaccine is 100% effective, and this is likely to be the same for HIV. Some people who receive a vaccine will not respond strongly enough to the vaccine and will not be protected, as in the case of the seasonal flu vaccine. But finding at least a partially effective vaccine remains of critical

importance for the HIV response, as all successful disease elimination strategies have included a vaccine among their arsenal.

The need for a vaccine against HIV

UNAIDS estimates that 1.8 million people became infected with HIV in 2017, 36.9 million people were living with HIV and 21.7 million were receiving antiretroviral therapy. Despite dramatic improvements in access to antiretroviral therapy, and evidence in some regions of the world that treatment scale-up has resulted in a reduction in new HIV infections, there is still a need for a vaccine against HIV.

A model developed by the [International AIDS Vaccine Initiative](#) has estimated that even if the UNAIDS targets for treatment scale up are achieved by 2020, a vaccine that stopped 70% of infections would reduce new infections by 44% in the first 10 years after a projected introduction in 2027. By 2070, a vaccine that was 70% effective would reduce new infections by 78%.²

The model also found that a 70% effective vaccine would have a greater impact on new infections than pre-exposure prophylaxis (PrEP). The biggest reduction in new infections would be achieved by a combination of PrEP, universal antiretroviral treatment for people already living with HIV, and a vaccine.

This study assumed that a vaccine would only provide protection for five years before people needed a booster shot. The cost of administering such a vaccine would still be substantially lower than providing PrEP or HIV treatment. By preventing new infections and reducing the cost of prevention, an HIV vaccine would improve the sustainability of the HIV response.

Another modelling study found that a 50% effective vaccine would have the greatest impact in eastern and southern Africa. Even if these countries all achieved the UNAIDS targets for treatment scale up by 2020, the introduction of a vaccine would prevent approximately 7 million new infections by 2035.³

Challenges in HIV vaccine development

Researchers have been working on an HIV vaccine since the 1980s, but progress towards an effective vaccine has been much slower than anticipated.

Most vaccines against other diseases stimulate the production of antibodies that 'neutralise' viral infectivity, but in the case of HIV, neutralising antibodies do not clear the infection. This is because HIV reproduces so fast, and mutates so quickly, that antibodies produced against the virus quickly become ineffective against newer viruses. Millions of new viruses are produced each day and each one is slightly different from previous generations of the virus. Antibodies against HIV are only likely to be effective if they can bind to regions of the virus that vary little between viruses.

Another issue is that HIV has several sub-types which are concentrated in different regions of the world. For example, sub-type B is common in North America and Europe, but sub-type C is common in southern and eastern Africa. Any vaccine must either be effective against all sub-types or different vaccines must be developed against various sub-types.

A vaccine might also stimulate the production of immune system cells called T-lymphocytes that can clear HIV-infected cells. But HIV has also evolved to suppress some immune responses that are

important in the early stages of a viral infection.

Another challenge in vaccine development is finding efficient ways to deliver HIV proteins safely in ways that will allow the immune system to recognise HIV and respond to it without establishing an infection. HIV integrates into human cells and uses those cells to reproduce, so live or attenuated whole-virus vaccines are unsuitable for use in HIV. Instead, HIV proteins need to be engineered in ways that make them harmless but still recognisable to the immune system. These proteins or sequences of viral material must be delivered using a vector – another harmless virus such as canarypox or a common cold virus – which presents them to the immune system.

Researchers are still working to understand what they call the ‘correlates of protection’ – the immune system markers which show that a person is protected against HIV after vaccination. These measurements must be assembled from observations in clinical trials and animal studies. Progress towards identifying the correlates of protection has been slow due to a lack of animal models. Animals cannot be infected with the human immunodeficiency virus, so studies must be done in monkeys using the monkey equivalent SIV, or by using a construct called SHIV.⁴

Progress in developing an HIV vaccine

The first large HIV vaccine trial reported results in 2003. This trial tested a vaccine called AIDSVax which combined fragments of HIV’s gp120 surface protein from HIV sub-type B. The vaccine was designed to produce neutralising antibodies against gp120. The trial found that the vaccine offered no protection compared to a dummy vaccine. A trial of a vaccine using the same design, but combining gp120 sequences from sub-types A and E, also showed no protective effect.^{5 6}

A different vaccine strategy, using a vector virus to deliver HIV protein sequences to stimulate cellular immunity rather than antibody production, was tested in the STEP study. The trial vaccine used an adenovirus, a cause of common cold symptoms, as the vector. The STEP study was halted in 2007 after an analysis showed that the vaccine had not reduced the risk of infection.⁷

Subsequent analysis showed that people with the highest levels of pre-existing antibodies to adenoviruses had a higher risk of infection than people who received a dummy vaccine. The study results showed that more research was needed to develop vaccines to produce protective T-cell responses against HIV.

In 2009, the RV144 trial reported a modest reduction in the risk of infection in a trial using a prime-boost vaccine approach – the first trial ever to do so. The trial tested a vaccine approach in which people received a ‘prime’ dose of ALVAC-HIV, a canarypox vector containing three genetically-engineered sequences of HIV genes, and a booster dose using the AIDSVax gp120 vaccine. The ‘prime’ vaccine was designed to stimulate cellular immune responses, while the aim of the booster was to stimulate neutralising antibody responses. The prime-boost vaccination reduced the risk of infection by 31%, a significant reduction in risk.⁸

The RV144 trial result was a surprise to vaccine researchers. They had assumed that one effect of the vaccine would be to produce strong CD8 T-cell responses that would result in lower viral load in those who did become infected despite vaccination. But the vaccine did not produce strong CD8 T-cell responses, nor did it produce strong antibody responses.

The results of the RV144 trial show the challenge scientists face in trying to determine how to

measure whether a potential vaccine is worth testing in large clinical trials. The trial results suggest that a vaccine may need to stimulate antibody and cellular immune responses to HIV, and that cellular responses are dependent on specific antibody responses.⁹

A version of the vaccine tested in the RV144 trial was subsequently tested in South Africa in the HVTN 100 study. This vaccine contained sequences of the HIV sub-type C virus that is most commonly found in southern Africa and used a different dosing schedule designed to produce stronger responses to the vaccine. The study found that the vaccine produced strong antibody responses to HIV envelope proteins. The vaccine produced especially strong antibody responses of a type that correlated with protection against infection in the RV144 study.¹⁰

Current vaccine trials: Uhambo and Imbokodo

The modified RV144 vaccine tested in the HVTN100 trial is now being tested in a large phase 3 study, HVTN 702 (also known as Uhambo), in southern Africa. The study, which will recruit 5,400 people, is designed to show whether the vaccine reduces the risk of infection by at least 50% and extends the period of protection compared to the RV144 study. The results of the study are expected by 2021.¹¹

A second large vaccine study, HVTN 705 (also known as Imbokodo), is testing a prime-boost vaccine of a different design that has shown promising effects in preliminary studies. The vaccine to be tested in HVTN 705 combines a 'prime' vaccine that uses an adenovirus vector to deliver 'mosaic' proteins designed to produce responses against a wide range of viruses, and an HIV subtype C booster designed to stimulate the production of antibodies against the HIV envelope protein gp140.

This vaccine, which has been developed by the pharmaceutical company, Janssen, is being tested on 2,600 women aged 18 to 35 in southern and eastern Africa. The results are expected by 2022.¹²

If the vaccine tested in the HVTN 702 study proves effective, this will not lead to immediate licensing and roll-out of the vaccine. Instead, researchers say they will use the results of the study to improve the vaccine and to learn how to scale up vaccine manufacturing.¹³ The same goes for the HVTN 705 study.

Future approaches to HIV vaccine development

Several other promising approaches to HIV vaccine development are also being pursued.

Broadly neutralising antibodies can recognise many different strains of HIV. They target regions of HIV that do not mutate and vary little between viral subtypes. Less than 20% of people living with HIV make these antibodies. Broadly neutralising antibodies can be isolated and reproduced in the laboratory. Infusions of broadly neutralising antibodies are being tested as an HIV prevention method in a clinical trial, AMP, which is due to report results in 2020. Several other studies are testing different combinations of broadly neutralising antibodies.¹⁴

Other studies are testing HIV DNA vaccines. DNA vaccines are designed to overcome the problems of

using whole viruses or attempting to engineer recombinant virus sequences that can stimulate strong immune responses. DNA vaccines deliver DNA that contains code for specific viral proteins. Cells take up the DNA and produce the proteins and these are recognised by the immune system, leading to stronger immune responses than vaccines based on viral vectors. Several DNA vaccines are in early-stage human studies.¹⁵

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Ethical issues in vaccine development

In addition to the ethical issues raised by all forms of medical research, HIV vaccine trials raise several of their own.

Participants in trials need to have access to the standard of care in addition to the intervention being tested. The standard of care in HIV prevention is changing rapidly as more and more countries begin to make PrEP available. The future availability of a vaginal ring containing an antiretroviral drug will also affect the standard of care for women in vaccine trials.

Receiving an experimental vaccine may reduce the benefit that trial participants might get from a future, more effective vaccine, and may also give participants the impression that they are protected against HIV. This false sense of security may lead participants to take risks during and after the trial that lead to HIV infection.

People who take part in vaccine trials and who receive the active vaccine are likely to test positive for HIV antibodies. Trial participants require confidentiality and protection against discrimination, just like people living with HIV.

Vaccine trials also raise issues regarding treatment for people who become infected despite vaccination. Trials are designed to measure viral load in people who become infected, to see whether the vaccine has any impact on the natural course of HIV after infection. But as guidelines now recommend treatment for everyone with HIV, how long is it ethical to delay treatment after infection during a vaccine trial? And, if treatment is provided immediately when it is not available to others outside the trial, does this encourage to participate in the study?¹⁶

What happens if a highly effective vaccine is discovered?

An optimistic forecast of HIV vaccine availability is that one might be available by 2030. A more pessimistic view is that it may take 20 to 30 years to develop a vaccine that is judged to be effective enough to justify the financing of widespread vaccination campaigns in regions where HIV is endemic.

The critical determinant of the speed at which a vaccine will become available is the question of the minimum efficacy needed to make it cost-effective.

No vaccine protects everyone who receives it. The effectiveness of the seasonal flu vaccine varies enormously from year to year. The question for HIV vaccine researchers is: should a vaccine that reduces the risk of infection by 50% be implemented immediately, or should research continue in the hope that a vaccine that is 90% effective will be possible a few years later?

Modelling by the International AIDS Vaccine Initiative indicates that even when a vaccine is only 30% effective, it would reduce new infections by 44% over 10 years when used alongside universal treatment and PrEP.¹⁷ A review of all studies of HIV vaccine cost-effectiveness found that the efficacy of a vaccine was much less important than the cost of HIV treatment or the level of HIV transmission in determining whether a vaccine would be cost effective.¹⁸ If a vaccine is judged ready for widespread human use, adequate finance will be needed to guarantee purchases of the vaccine. Manufacturers will need guarantees to scale up production. Once production processes have been inspected to ensure consistent high-quality batches of vaccine, the vaccine will need to be licensed in every country where it is to be used.

National authorities will also need to decide who to prioritise for vaccination. These decisions are likely to be taken on a country-by-country basis and will depend on the efficacy and cost of the vaccine, as well as the rate of transmission. For example, some countries with high HIV incidence in young women may decide to prioritise adolescent girls and young women. In other countries, with concentrated epidemics, the priority groups might be people who inject drugs, sex workers or men who have sex with men.

Achieving an effective vaccine for HIV

An HIV vaccine is a more realistic prospect today than a decade ago. Studies have shown some evidence that current vaccine designs can produce strong immune responses that protect some people against HIV infection. Results from larger studies between 2021 and 2022 are likely to provide much more information about the timescale for achieving an effective vaccine.

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