



Update on HIV Vaccine Research

The rapid development of effective vaccines against Coronavirus Disease 2019 (COVID-19) has led to some questions about why it's taking so long to achieve similar success against HIV. The crux of the problem is that HIV is a very different virus from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19.

HIV is a retrovirus that causes a persistent rather than transient infection. HIV persists by copying the RNA that it's made from into DNA, and then integrating this viral DNA into the DNA of the cells that it infects. Once the HIV DNA is inserted into the cell, there is a genetic blueprint for making more HIV in the body that typically persists for life. This means that an HIV vaccine needs to create immune responses capable of blocking the virus's entry into the body fast enough to prevent the integration of HIV DNA into the DNA of any cells.

SARS-CoV-2 is a coronavirus that is also made of RNA, but it lacks the ability to copy itself into DNA and integrate into the DNA of a cell. Even in unvaccinated people who get infected, SARS-CoV-2 infection is therefore relatively transient (even though there can be long-term health effects from the infection in some cases).

HIV also mutates more rapidly than SARS-CoV-2, making it more of a moving target for immune responses. Unlike HIV, coronaviruses like SARS-CoV-2 have what's called a "proofreading" mechanism that makes their genetic makeup more stable and less prone to mutation than HIV (although mutations do still occur, leading to SARS-CoV-2 variants).

The outer envelope of HIV has evolved highly effective mechanisms for fending off antibodies, primarily involving constant mutation and a shield formed of sugar molecules (as a loose analogy, imagine a shroud of cotton candy). This HIV trait makes it very difficult to induce effective antibody responses (referred to as neutralizing antibodies) with vaccination. The outer spike protein of SARS-CoV-2 is thankfully very susceptible to neutralizing antibodies, which are readily induced by including a copy of the spike protein in COVID-19 vaccines.

Despite the challenges posed by HIV for vaccine development, researchers have been working to address the problem since the virus was first discovered. As yet,

no vaccine has demonstrated any ability to create what is believed to be the ideal type of immune response: broadly neutralizing antibodies (bNAbs), which have the ability to strongly block infection by multiple diverse variants of HIV. Research in this area remains ongoing.

Five different candidate HIV vaccine regimens have been tested in seven large trials that assessed whether they could protect against HIV infection (efficacy trials), but marginal evidence of a reduction in the rate of HIV infection was only seen in one trial (see table). A follow-up trial designed to try to improve upon this result was not successful, with no efficacy observed.

HIV vaccines tested to date weren't able to induce neutralizing antibody responses, but instead were designed to induce other types of immune responses that might have a capacity to block or suppress HIV. These immune responses include T cells and "non-neutralizing" antibodies that may have the capacity to promote killing of HIV-infected cells.

There are now two ongoing efficacy trials of a vaccine regimen designed to induce both T-cell and non-neutralizing antibody responses to a broad range of HIV variants from multiple different subtypes (HIV subtypes are groups of closely related viruses found in different regions of the globe, for example subtype B is most common in the Americas, while subtypes A and C predominate on the African continent). The HIV components in the vaccines are called mosaic antigens because they represent an amalgam derived from many virus subtypes.

The vaccine regimen is manufactured by Johnson & Johnson. The mosaic antigens are delivered into the body as proteins with an adjuvant (a substance designed to provoke an immune response to the protein) and by an adenovirus serotype 26 (Ad26) vector (the same delivery platform used for the company's authorized COVID-19 vaccine).

One of the trials, named Imbokodo (or HVTN 705/HPX2008), has recruited 2,637 heterosexual cisgender women at risk of HIV infection in South Africa, Malawi, Mozambique, Zambia, and Zimbabwe. The trial is nearly complete, and results are anticipated in 2021. The second trial, Mosaico (or HVTN 706/HPX3002), is taking place in

Argentina, Brazil, Italy, Mexico, Peru, Poland, Spain, and the United States and is recruiting 3,800 cisgender men and transgender people who have sex with cisgender men and/or transgender people. Enrollment for Mosaico is near completion, and results are due in 2024.

The results of these trials will represent a significant milestone for HIV vaccine research. If no efficacy is documented, it will greatly diminish the prospects for a vaccine protecting against HIV infection without inducing bNAbs.

All hope will not be lost, however. The identification of a growing number of bNAbs produced by some rare individuals with HIV infection has helped provide scientists with a roadmap for how this type of response might be induced by vaccines (see separate handout). Clinical trials are underway looking at various approaches for triggering the expansion of certain immune system cells—known as B cells—that may represent a starting point for bNAb production.

These results have generated some excitement in the media, but the reporting has not always been accurate—additional steps need to be figured out in order for bNAbs to be generated. Encouragingly, the messenger RNA (mRNA) technology used in successful COVID-19 vaccines may help accelerate the identification of substances that can guide B cells toward the end goal of generating bNAbs.

A novel approach that has just entered human clinical trials uses a weakened form of cytomegalovirus (CMV), a common virus, to deliver HIV antigens. The vaccine has shown a consistent ability to prevent a proportion (about 50%) of very virulent simian immunodeficiency virus (SIV) infections in macaque monkeys (SIV is a simian relative of HIV used in animal experiments). The efficacy is associated with the induction of unusual CD8 T-cell responses, and it remains to be seen if the vaccine can create similar responses in people.

Table: Completed HIV vaccine efficacy trials

TRIAL	VACCINE	LOCATION	POPULATION	RESULT
VAX004	Bivalent clade B HIV gp120 protein in alum adjuvant	United States, Europe	5,147 men who have sex with men (MSM) and 300 cisgender women	No efficacy
VAX003	Bivalent CRF_01AE/B HIV gp120 protein in alum adjuvant	Thailand	Injection drug users	No efficacy
HVTN 502 (STEP)	Adenovirus type 5 (Ad5) clade B HIV Gag/Pol/Nef	United States	MSM, heterosexual men and women	No efficacy; increased infection in vaccinees
HVTN 503 (Phambili)	Ad5 clade B HIV Gag/Pol/Nef	South Africa	Heterosexual men and women	No efficacy; increased infection in male vaccinees
RV144	ALVAC with HIV Gag/Pro/Env; bivalent CRF_01AE/B HIV gp120 proteins in alum adjuvant	Thailand	Men and women recruited from the community without regard to HIV risk (i.e., community risk)	Estimated 31.2% vaccine efficacy (reduced the rate of HIV infection by about a third compared with placebo shots)
HVTN 505	DNAs with clade B HIV Gag/Pol/Nef and DNAs with clade A, B, and C HIV Envs; Ad5 with gag/pol and clades A, B, and C HIV Envs	United States	MSM and transgender women (Ad5 seronegative, circumcised)	No efficacy
HVTN 702	ALVAC-HIV + subtype C gp120 protein in MF59 adjuvant	South Africa	Heterosexual cisgender men and women	No efficacy

Table adapted from Haynes B. New approaches to HIV vaccine development. Curr Opin Immunol. 2015 Aug;35:39–47.

AUGUST 2021
Made for the *We The People Research Cohort*

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