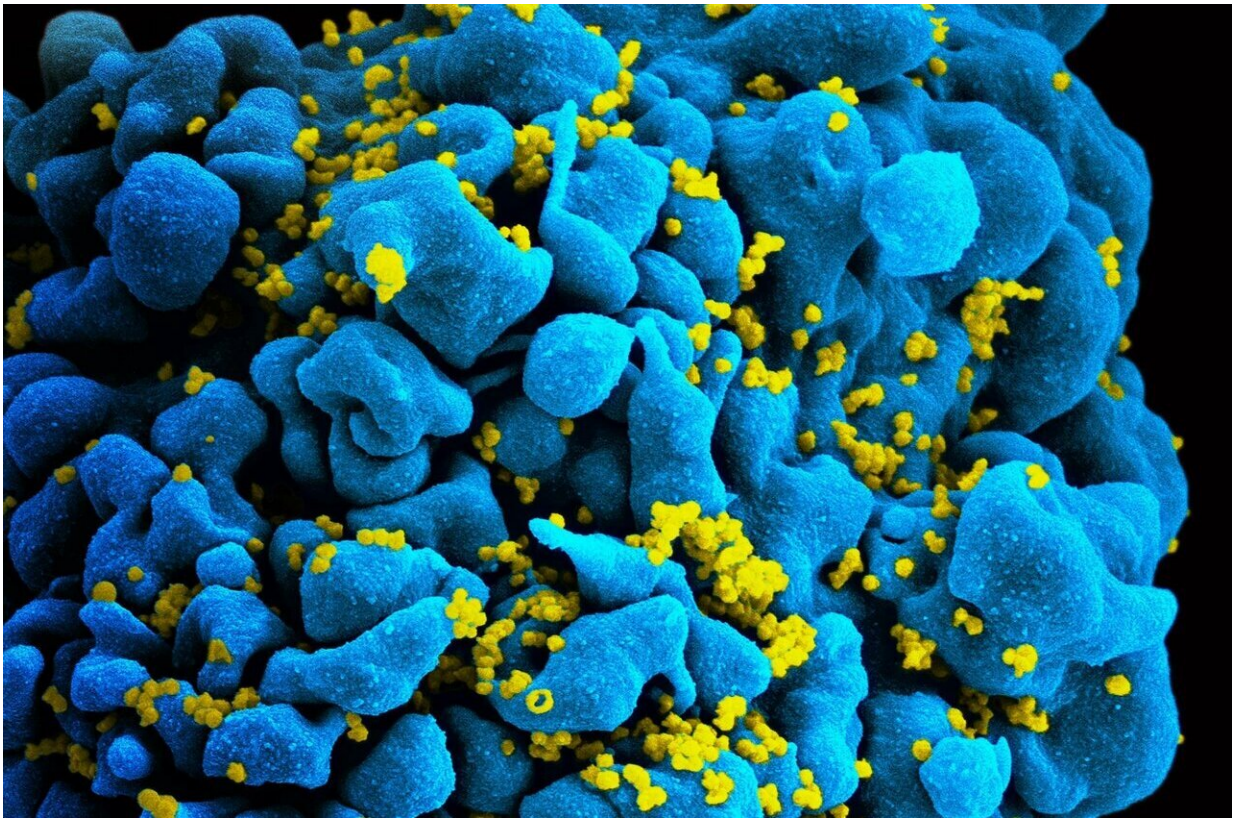
# Drug-delivery technology leads to sustained HIV antibody production

March 9 2020



Scanning electromicrograph of an HIV-infected T cell. Credit: NIAID

A new approach to direct the body to make a specific antibody against HIV led to sustained production of that antibody for more than a year among participants in a National Institutes of Health clinical trial. This

drug-delivery technology uses a harmless virus to deliver an antibody gene into human cells, enabling the body to generate the antibody over an extended time. With further development, such a strategy could be applied to prevent and treat a wide variety of infectious diseases, according to the study investigators.

Researchers from NIH's National Institute of Allergy and Infectious Diseases (NIAID) reported the findings on March 9 in an oral presentation at the 2020 Conference on Retroviruses and Opportunistic Infections (CROI).

Antibodies are immune system proteins that help prevent or clear infections. Traditional vaccines induce the immune system to generate protective antibodies. Another approach to preventing infections is to deliver monoclonal antibodies—preparations of a specific antibody designed to bind to a single target—directly into people. Monoclonal antibodies also are used therapeutically, with many already approved for treating cancer, autoimmune diseases and other conditions and others being evaluated for treatment of infectious diseases, such as Ebola virus disease.

Administering proteins to people requires periodic injections or infusions to retain protective or therapeutic levels, which can be challenging, particularly in resource-limited settings. Delivery of antibody genes using a virus as a carrier, or vector, offers a potential alternative.

"Monoclonal antibodies hold enormous promise for preventing and treating both established and emerging infectious diseases," said NIAID Director Anthony S. Fauci, M.D. "Novel delivery platforms such as viral vectors could facilitate the future development and deployment of antibody-based prophylaxis and therapy, and these findings are a promising first step in that direction."

The drug-delivery system developed by scientists at NIAID's Vaccine Research Center (VRC) uses adeno-associated virus serotype 8 (AAV8) to deliver an antibody gene. AAVs—small viruses that do not cause disease in humans—have proven to be safe, well-tolerated vectors for gene therapy. In a previous study in animal models, VRC researchers found that using AAV8 to deliver genes for antibodies against simian immunodeficiency virus (SIV), the monkey equivalent of HIV, led monkeys to safely produce high levels of anti-SIV antibodies and protected them from acquiring SIV.

Building on this preclinical work, researchers designed a Phase 1 clinical trial known as VRC 603. It aims to assess the safety and tolerability of an AAV8 vector carrying an anti-HIV antibody gene in adults living with well-controlled HIV, and to evaluate whether it could cause human cells to produce the antibody. The vector carries the gene for an anti-HIV monoclonal antibody called VRC07, which was originally isolated from the blood of a person with HIV.

VRC07 is a broadly neutralizing antibody (bNAb), meaning it can stop a wide range of HIV strains from infecting human cells in the laboratory. Other clinical studies are underway to determine whether bNAb infusions can protect humans from acquiring HIV. Scientists also are evaluating whether combinations of HIV bNAbs can suppress the virus in people living with HIV.

The CROI presentation by Joseph P. Casazza, M.D., Ph.D., principal investigator of VRC 603, described initial results from the first eight participants in the ongoing trial, which is being conducted at the NIH Clinical Center in Bethesda, Maryland. Each of these individuals, aged 30 to 60 years, received a single dose by intramuscular injection of one of three different dose levels of AAV8-VRC07. They continued taking daily antiretroviral therapy.

Following injection with AAV8-VRC07, all eight participants produced VRC07 at levels detectable in the blood. VRC07 production reached an early peak four to six weeks after injection, then decreased, and slowly began to increase again roughly 16 weeks after the injection. The researchers have monitored the five participants who received low or intermediate AAV8-VRC07 doses for one and a half to two years. For three of these five individuals, antibody levels one year after injection were higher than those observed at four to six weeks. The three volunteers who received the highest AAV8-VRC07 dose have so far been monitored for five months to one year. Two produced VRC07 at concentrations higher than those seen in the low and intermediate dose groups.

Study participants have not experienced any major side effects due to AAV8-VRC07. Some volunteers experienced transient mild tenderness at the injection site or mild muscle pain.

"To the best of our knowledge, this marks the first time that an AAV-based technology to deliver an antibody gene has resulted in safe and sustained levels of that antibody in blood," said NIAID VRC Director John Mascola, M.D. "We hope that further development of this technology will yield a drug-delivery strategy applicable to a broad range of infectious diseases."

Administration of monoclonal antibody-based therapies sometimes results in a person's immune system developing antibodies against the therapy. Only three of the eight VRC 603 participants developed antibodies against VRC07; it is not yet clear whether these anti-drug antibodies could reduce VRC07's ability to neutralize HIV. The VRC 603 participants' HIV was kept under control with continued antiretroviral therapy during the trial.

The concentrations of VRC07 observed in the study participants were

lower than the antibody concentrations observed in animal studies of the AAV8-based technology. The VRC researchers are analyzing data from VRC 603 to better understand the factors that determine how much bNAb is produced by human cells. They also are continuing to monitor the VRC 603 participants and to enroll new volunteers into the trial.

**More information:** JP Casazza et al. Durable HIV-1 antibody production in humans after AAV8-mediated gene transfer. Oral presentation at the 2020 Conference on Retroviruses and Opportunistic Infections (CROI). Presented March 9, 2020.

Provided by NIH/National Institute of Allergy and Infectious Diseases