# HIV Vaccine Fails in Large Clinical Trial

The vaccine regimen tested in the Imbokodo trial was similar to the J&J COVID-19 vaccine, but an mRNA approach may hold more promise.

August 31, 2021 By Liz Highleyman

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An experimental vaccine regimen did not protect young women from acquiring HIV in the large Imbokodo trial in Africa, Johnson & Johnson announced today. The vaccine reduced the risk of infection by 25%, far below the 50% effectiveness threshold researchers were aiming for, adding to a long string of disappointments in HIV vaccine research.

> We knew it wasnt going to be easy...still very hard to get this news though. We will just have to keep pushing on. #HIVVaccines Johnson & Johnson and Global Partners Announce Results from Phase 2b Imbokodo HIV Vaccine Clinical Trial in Young ... https://t.co/sG5qzfrzzH
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> — Linda-Gail Bekker (@LindaGailBekker) August 31, 2021

"The development of a safe and effective vaccine to prevent HIV infection has proven to be a formidable scientific challenge," National Institutes of Allergy and Infectious Diseases director Anthony Fauci, MD, said in a statement. "Although this is certainly not the study outcome for which we had hoped, we must apply the knowledge learned from the Imbokodo trial and continue our efforts to find a vaccine that will be protective against HIV."

The parallel Mosaico trial, which is testing a similar vaccine regimen in gay and bisexual men and transgender women, is currently underway and will continue. But some experts think more sophisticated approaches will be needed—and others question whether an HIV vaccine is even a

realistic goal given the very good effectiveness of pre-exposure prophylaxis (PrEP) using pills or long-acting injections.

While highly effective COVID-19 vaccines were developed in less than a year, HIV vaccines are more challenging, and the candidates studied to date have been much less successful.

So far, only one study—the RV144 trial in Thailand—has shown any effectiveness in preventing HIV. That trial tested a vaccine dubbed ALVAC-HIV, which used a canarypox virus vector to deliver DNA instructions for HIV proteins, plus another vaccine that contains genetically engineered HIV gp120 envelope proteins. In 2009, researchers reported that this prime-boost combination reduced new infections by 31%.

Following up on those findings, the Uhambo trial (HVTN 702) trial tested ALVAC-HIV plus a gp120 protein subunit vaccine, both adapted to target HIV subtype C, which is predominant in southern Africa. Although this regimen triggered potent antibody and T-cell responses, it did not prevent HIV—the risk of acquiring the virus was essentially the same in the vaccine and placebo groups—and the study was halted ahead of schedule in February 2020.

That left just two large HIV vaccine trials underway, both testing a primer vaccine dubbed Ad26.Mos4.HIV that uses an adenovirus type 26 vector (a common cold virus) similar to the one used in the J&J COVID-19 vaccine. The vector virus carries a computer-designed mosaic of antigens from multiple HIV strains found around the world. The regimen also includes a second vaccine that contains soluble gp140 envelope proteins. Earlier studies showed that this combination induced strong antibody and T-cell responses and protected monkeys exposed to SIV, HIV's simian cousin. However, the vaccines did not generate broadly neutralizing antibodies that target a hidden region of HIV's envelope protein that differs little across diverse viral strains.

The Phase IIb Imbokodo (HVTN 705) trial, started in 2017, recruited more than 2,600 young women ages 18 to 35 at high risk for HIV in five countries in sub-Saharan Africa. The study was supported by Johnson & Johnson, the National Institute of Allergy and Infectious Diseases, the Bill & Melinda Gates Foundation and the HIV Vaccine Trials Network.

The study participants were randomly assigned to receive four doses of the Ad26.Mos4.HIV vaccine or placebo injections over the course of a year. At the third and fourth visits, those in the vaccine group also received a vaccine containing HIV subtype C gp140 proteins.

The vaccine regimen "did not provide sufficient protection against HIV infection," according to a Johnson & Johnson press release. In a primary analysis conducted two years after the first dose, 51 of the participants who received the vaccines and 63 who received the placebo acquired HIV, for a vaccine efficacy 25.2%. The difference was not statistically significant, meaning it could have been due to chance. The vaccines had a "favorable safety profile" with no serious adverse events.

Based on these findings, the Imbokodo study will not continue. Participants will be notified of the results and told whether they were in the vaccine or placebo group. Further analysis of the data is ongoing, and researchers hope it will shed new light on the immunological correlates of protection

against HIV.

“This has been a well-designed and conducted study, and there will be critical data coming from it, including probing the immune response generated by the vaccine, that will help guide future efforts,” study protocol co-chair Susan Buchbinder, MD, director of the HIV Research Section at the San Francisco Department of Public Health, said in a statement from the International AIDS Society. “With the additional insights gained in the COVID-19 response, with concerted backing by funders and continued research, and with the political will needed, I am certain that an HIV vaccine is achievable.”

“HIV is a unique and complex virus that has long posed unprecedented challenges for vaccine development because of its ability to attack, hijack and evade the human immune system,” said J&J chief scientific officer Paul Stoffels, MD. “While we are disappointed that the vaccine candidate did not provide a sufficient level of protection against HIV infection in the Imbokodo trial, the study will give us important scientific findings in the ongoing pursuit for a vaccine to prevent HIV.”

So what’s next for HIV vaccine research?

The parallel Phase III Mosaico (HVTN 706) study, started in 2019, has recruited approximately 3,800 gay and bisexual men and transgender people in North America, South America and Europe. It is testing a similar vaccine regimen of Ad26.Mos4.HIV plus a mixture of HIV envelope proteins, rather than just the sybtype C proteins in the Imbokodo regimen. An independent Data and Safety Monitoring Board determined that the two trials are different enough that it would be useful and not unethical to continue Mosaico. Results are expected in 2024.

Researchers are also exploring novel approaches, including the messenger RNA (mRNA) technology used for the Pfizer-BioNTech and Moderna COVID-19 vaccines. One recent study showed that an experimental mRNA vaccine that delivers instructions for HIV and SIV proteins triggered production of neutralizing antibodies and protected monkeys from infection. The International AIDS Vaccine Initiative and Moderna recently launched a Phase I study of a vaccine approach known as germline targeting, which trains immature B cells in a stepwise fashion to generate broadly neutralizing antibodies.

Join AVAC for a webinar on Sept 9 at 10am ET discuss the Imbokodo study, the large-scale #HIVvaccine proof-of-concept trial also known as HVTN 705/ HPX2008, and the implications for the HIV vaccine field. https://t.co/JJO5rGx0O3 @HelpEndHIV @JNJNews

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— AVAC (@HIVpxresearch) August 31, 2021

“This is in no way the end of the search for an HIV vaccine,” Mitchell Warren, executive director of the HIV prevention advocacy group AVAC, said in a statement. “We need an HIV vaccine to provide a durable end to the HIV pandemic, but we can’t wait for a vaccine. Now is the time to go all in on providing comprehensive HIV prevention options that already exist and the programs needed to support people in using their chosen options, while also reengaging in vaccine research. If we’ve learned one lesson from the COVID-19 response, it is that political will, sufficient funding and unprecedented cooperation in the face of a global threat is possible. HIV has been for decades—and remains—a global threat; it is past time to act boldly to confront it.”

AVAC will host a webinar on September 9 at 10 a.m. ET to discuss the Imbokodo results and their implications for the HIV vaccine field.

Updated 9/1/21 to include comments from Susan Buchbinder, MD.

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