Once-Promising Vaccine Regimen Fails to Prevent HIV

People who received a canarypox vector vaccine regimen were no less likely than placebo recipients to acquire HIV.

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An experimental vaccine regimen did not protect people from acquiring HIV in a large clinical trial in South Africa, an international team of scientists reported recently in The New England Journal of Medicine. These results add to a long string of disappointments in HIV vaccine research.

“The high HIV-1 incidence that we observed in our trial illustrates the unrelenting aspect of the epidemic, especially among young women,” Glenda Gray, MBBCH, of Fred Hutchinson Cancer Research Center in Seattle, and the HVTN 702 team wrote. “More than ever, an effective vaccine to prevent HIV-1 acquisition in diverse populations is needed.”

While highly effective COVID-19 vaccines were developed in under a year, the history of HIV vaccine research has been far less successful. In April 1984, Health and Human Services Secretary Margaret Heckler predicted that an HIV vaccine could be ready for testing in about two years—but we’re still waiting.

Many different approaches have been explored in the long quest for an HIV vaccine. 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 uses a canarypox virus vector to deliver DNA instructions for HIV proteins, plus another vaccine called AIDSVAX that contains genetically engineered gp120 envelope proteins from different strains of HIV. In 2009, researchers reported that this prime-boost combination reduced new infections by 31%.

Following up on those findings, the Phase II/III Uhambo trial (HVTN 702) tested ALVAC-HIV plus a gp120 protein subunit vaccine, both adapted to specifically target HIV subtype C, which is predominant in southern Africa. The protein subunit vaccine also contained a new adjuvant (MF59) intended to stimulate a stronger immune response. This regimen was shown to trigger potent antibody and T-cell responses in an earlier study.

Starting in 2016, the HVTN 702 team enrolled 5,404 people at risk for HIV at 14 sites in South Africa. A majority of the participants (70%) were women. The median age was 24 years, with the men being a bit older than the women. About 15% lived with a spouse or primary partner, about

20% reported exchanging sex for money or gifts, most said they used condoms some of the time (about 75%) or never (about 18%) and 30% of the women and 18% of the men were diagnosed with sexually transmitted infections at enrollment.

Although the participants were offered free pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP), only 3% of women and men reported that they used PrEP and just 2% of the women and 5% of then men reported using PEP after a potential HIV exposure.

The study participants were randomly assigned to receive the vaccine combination or placebo injections. ALVAC-HIV was administered at study entry and one month later, followed by four booster shots of the gp120 protein vaccine at months 3, 6, 12 and 18.

In February 2020, the trial was halted ahead of schedule after an interim review found that the vaccine regimen was not effective. Over two years of follow-up, 138 participants in the vaccine arm and 133 people in the placebo arm were diagnosed with HIV. The incidence rates in the two groups were 3.4 and 3.3 per 100 person-years, respectively; however, the combined incidence in both groups was substantially higher among women (about 4.3) compared with men (1.3).

The overall hazard ratio was 1.02, meaning the likelihood of acquiring HIV was essentially the same in the vaccine and placebo groups. The lack of efficacy was similar for women and for men (hazard ratios of 1.03 and 0.99, respectively). What's more, among the people who did become infected, viral load was not reduced in the vaccine group.

The vaccine regimen was generally safe and well tolerated. The most common side effect was mild pain or tenderness at the injection site, which was more frequent in the vaccine group compared with the placebo group.

Speculating about the reasons for the different outcomes in HVTN 706 and RV144, the researchers noted that the background HIV incidence was much higher in South Africa compared with Thailand (4.2% versus 0.3% among women in the placebo groups of the two studies). The similar but not identical vaccine regimens elicited somewhat different immune responses (for example, antibodies targeting different parts of the HIV envelope protein). Given the high prevalence of sexually transmitted infections, it's likely that genital tract inflammation contributed to the high HIV rate. The diversity of HIV subtype C in South Africa while HVTN 702 was underway was greater than the diversity of subtype A/E in Thailand 15 years earlier. Finally, genetic differences between the South African and Thai populations might have played a role.

"Thus, isolating which factor or combination of factors is responsible for the different efficacy results in the two trials will be challenging, given the differences between the vaccines and the immune responses they generated, along with the differences in the levels of viral exposure, the extent of matching between the vaccines and the exposing viruses, and in host genetics and other host factors," the study authors wrote.

Commenting on the interim results when the trial was halted last year, National Institute of Allergy

and Infectious Diseases director Anthony Fauci, MD, said in a press release: “An HIV vaccine is essential to end the global pandemic, and we hoped this vaccine candidate would work. Regrettably, it does not. Research continues on other approaches to a safe and effective HIV vaccine, which I still believe can be achieved.”

The latest disappointment leaves just two large HIV vaccine trials underway. Imbokodo (HVTN 705), started in 2017, has recruited more than 2,600 young women at high risk for HIV in southern Africa. Mosaico (HVTN 706), started in 2019, aims to recruit 3,800 cisgender gay and bisexual men and transgender people in North America, South America and Europe. Results are expected in 2022 and 2024, respectively.

Both studies are testing a primer vaccine dubbed Ad26.Mos4.HIV that uses an adenovirus type 26 vector similar to the one used in the Johnson & Johnson COVID-19 vaccine. The vector virus carries a computer-designed mosaic of antigens derived from multiple HIV strains found around the world. Previous studies found that the vaccine combo induced strong antibody and T-cell responses in humans and protected monkeys exposed to SIV, HIV’s simian cousin. But as past experience shows, promising responses in early studies don’t necessarily translate into HIV prevention in larger trials.

While these trials are underway, researchers are exploring novel approaches for HIV vaccines, 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 envelope proteins from three different subtypes of HIV plus an SIV protein triggered production of neutralizing antibodies and protected monkeys from infection.

Another approach aims to prime the immune system to produce broadly neutralizing antibodies against HIV. One reason HIV is so hard to prevent is that it mutates rapidly, creating a wide range of viral variants. These specialized antibodies target conserved and partially hidden regions of HIV’s envelope protein that differ little across diverse strains.

Just as HIV research laid the groundwork for COVID-19 vaccines, lessons learned from COVID-19 will hopefully further the quest for an HIV vaccine. “Advances in HIV vaccine science have literally paved the way for SARS-CoV-2 vaccines,” Fauci told reporters at this year’s virtual HIV Research for Prevention Conference. "What goes around comes around, and I expect this to feed back into HIV vaccine development.”

Click here to read the full HVTN 706 study report.

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