Where Are We Now With HIV Vaccines?

Researchers are exploring novel strategies to help the immune system produce broadly neutralizing antibodies.

March 19, 2023 By Liz Highleyman

The closure of the last large HIV vaccine trial is a disappointment, but the pipeline of more sophisticated prevention approaches is robust, experts said during a special session at the 30th Conference on Retroviruses and Opportunistic Infections (CROI). The trial should not be considered a failure, according to Lawrence Corey, MD, of the Fred Hutchinson Cancer Center in Seattle: We did get an answer, but it wasn't the one we wanted.

Susan Buchbinder and Lawrence Corey at CROI 2023Liz Highleyman

As previously reported, the Phase III Mosaico study was discontinued in January after interim results showed that Johnson & Johnson's experimental vaccine regimen did not reduce the risk of HIV acquisition for gay men and transgender women. The results were not surprising, as a parallel trial called Imbokodo was halted in early 2021 after interim results showed that a similar vaccine regimen did not adequately protect young women in Africa.

Mosaico enrolled some 3,900 cisgender men who have sex with men and transgender women in North and South America and Europe. All were offered oral pre-exposure prophylaxis (PrEP), and

only those who declined were included in the study.

Half of the participants in both Mosaico and Imbokodo received four doses of a vaccine dubbed Ad26.Mos4.HIV that uses an adenovirus type 26 vector—the same one used for the J&J COVID-19 vaccine—to deliver a computer-designed mosaic of antigens from multiple HIV strains. Imbokodo participants also received two doses of a second vaccine containing gp140 envelope proteins from HIV clade C, while Mosaico participants got two doses of a second vaccine that contained a mosaic of gp140 proteins from different strains. The other half received an equal number of placebo injections.

Mosaico study cochair Susan Buchbinder, MD, of the University of California San Francisco and the San Francisco Department of Public Health, reported that while the vaccine regimen was safe and well tolerated, the HIV incidence rate was exactly the same—113 people, or 4.1 new cases per 100 person-years—in both the vaccine and the placebo groups.

HIV incidence decreased with age, falling from 5.9 cases in the vaccine group and 5.1 cases in the placebo group among people ages 18 to 20 down to 2.6 cases per 100 person-years among those ages 45 to 60. More than 80% of the study participants were enrolled in Latin America, where the incidence rates were 4.8 and 4.7 cases per 100 person-years, respectively, in the vaccine and placebo groups. However, incidence was much lower for the 192 participants in the United States: 0 in the vaccine group and 1.3 per 100 person-years in the placebo group.

“Despite ongoing risk reduction counseling and linkage to PrEP, HIV incidence, particularly in young participants in Latin America, was very high,” Buchbinder and colleagues concluded. “This is a population in great need of additional effective HIV prevention modalities.”

What’s Next for HIV Vaccine Research?

Mosaico was the last large trial testing a more traditional vaccine for HIV prevention. Most experts now think more sophisticated approaches will be needed, several of which are in early studies. “Despite the disappointment, it’s a very vibrant time in HIV vaccine research,” Buchbinder said at a CROI media briefing.

Corey said that the science of HIV vaccines is “terrifically fascinating” and “things look good for immunological approaches to HIV prevention.” However, in what was no doubt an understatement, he cautioned that novel vaccine approaches will be “a little bit more complicated” and are going to “take us a little time.”

Most people living with HIV do produce antibodies against the virus, but they are narrowly targeted and don’t keep up with viral mutation. However, a small proportion of individuals produce broadly neutralizing antibodies (bnAbs) that target hidden regions of HIV’s outer envelope that don’t change much as the virus evolves.

Early research showed that a vaccine regimen similar to the ones tested in Mosaico and Imbokodo induced potent antibody and T-cell responses that protected monkeys exposed to SIV, HIV’s simian

cousin. But the vaccines generated only non-neutralizing antibodies, and researchers now think bnAbs will be the key to broad protection.

The large Antibody Mediated Prevention (AMP) trials showed that although a bnAb dubbed VRC01 did not reduce the likelihood of HIV acquisition overall, the risk dropped by 75% for people who were exposed to HIV strains that are susceptible to this antibody. Unfortunately, some 70% of HIV strains were resistant to VRC01, suggesting that a cocktail of different bnAbs may be needed.

Another approach is to help the immune system produce bnAbs. One strategy, known as germline targeting, uses a series of vaccines in a stepwise manner to encourage the development of specialized B cells that are then trained in lymph nodes to produce effective antibodies. In a small Phase I study (IAVI G001), all but one of the 36 participants who received a vaccine containing an immunogen made up of 60 engineered copies of HIV's gp120 envelope protein developed specialized precursor B cells. After a booster, these cells produced antibodies with greater affinity for the HIV proteins. The IAVI G002 trial, now underway, is using Moderna's mRNA technology to speed up production of successive versions of primer and booster vaccines.

Making an HIV vaccine is hard, but it is still necessary, Corey said, as we have never controlled an infectious disease at the population level without a vaccine.

Buchbinder and Corey both noted that we could not have had such rapid COVID vaccine development without decades of HIV vaccine research. "The HIV vaccine infrastructure was the NASA of COVID-19 vaccine development," Corey said. Now, the lessons learned from COVID may contribute to the quest for effective HIV vaccines.

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In this video from HIV.gov, Carl Dieffenbach, PhD, director of the Division of AIDS at the National Institute of Allergy and Infectious Diseases, discusses the Mosaico trial results and future directions for HIV vaccine research.

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