Studies Show Progress on Novel HIV Vaccine Approaches

Sophisticated vaccine strategies are making rapid progress, but it will likely be years before large trials show whether they can prevent HIV.

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Coinciding with HIV Vaccine Awareness Day, five research teams reported advances in novel HIV vaccine strategies designed to spur production of broadly neutralizing antibodies (bnAbs) that target hidden parts of the virus. While these findings are promising, they are still early steps in the years-long process of vaccine development.

Scientists have spent more than three decades and billions of dollars trying to develop vaccines to prevent HIV, with little success. Now that several traditional vaccine candidates have failed in large clinical trials, most researchers agree that more sophisticated approaches are needed.

People with HIV normally produce antibodies against the virus, but these usually target parts that are highly variable, so they don't recognize new viral mutations. Although only around 15% of individuals naturally produce bnAbs that target conserved parts of the virus—usually after infection is already established—most people possess rare immature B cells that have the potential to do so.

Typically, bnAbs emerge slowly over time as the virus and host evolve together. An initial neutralizing antibody response drives the emergence of viral escape variants, which in turn trigger new rounds of B cell activation, ideally leading to the production of bnAbs that recognize multiple variants. But HIV mutates so rapidly that it usually outstrips the immune system's ability to keep up. New vaccine approaches aim to make this process happen faster. Utilizing the messenger RNA (mRNA) technology used for COVID-19 vaccines is one way to speed things up.

Germline Targeting

An approach known as germline targeting uses a series of vaccines in a stepwise manner to encourage the development of specialized B cells and train them to produce bnAbs. An initial engineered immunogen primes precursor B cells to recognize HIV, after which they migrate to germinal centers to mature. Subsequent immunogens help the cells learn to recognize the right targets and produce bnAbs.

In 2022, William Schief, PhD, of IAVI's Neutralizing Antibody Center at the Scripps Research Institute, and colleagues described a novel immunogen, dubbed eOD-GT8 60mer, that elicits production of immature B cells that can learn to generate bnAbs similar to VRC01.This bnAb, which targets HIV's CD4 binding site, was isolated from an individual who naturally controlled the virus.

In the IAVI G001 trial, all but one of the 36 HIV-negative participants who received a vaccine containing the immunogen, which consists of 60 copies of an engineered version of HIV's gp120 envelope spike protein fused to a lipid nanoparticle, produced the desired precursor B cells. After a booster, these cells produced antibodies with greater affinity for the virus. These findings "demonstrate[d] for the first time that one can design a vaccine that elicits made-to-order antibodies in humans," Schief said at the time. The following year, researchers reported that the vaccine also stimulated strong CD4 helper T-cell responses against HIV in most study participants.

Those findings showed that the eOD-GT8 60mer primer vaccine kick-started the process of bnAb production. Now, two new papers describe the next steps. To shepherd maturing B cells toward producing the desired bnAbs, they are exposed to a series of booster immunogens that look more and more like real HIV envelop proteins.

In the first study, published in Science Immunology, researchers at Scripps and the Ragon Institute of Mass General, MIT and Harvard validated the efficacy of lipid nanoparticles containing mRNA that encodes instructions for eOD-GT8 60mer. Using humanized mice with three different B-cell lineages, they found that all the lineages could be simultaneously primed without competition, and three different booster immunogens encouraged precursor B cells to mature and produce VRC01-like bnAbs.

In the second study, published in Science Translational Medicine, the Scripps team, working with scientists at the National Institutes of Health's Vaccine Research Center and Moderna, designed and tested the first booster immunogen, dubbed core-g28v2 60mer. After an initial eOD-GT8 60mer primer vaccine, humanized mice received either core-g28v2 60mer, delivered as a protein or mRNA, or a placebo booster. The mice boosted with core-g28v2 60mer produced antibodies that were closer to VRC01-class bnAbs than mice that got the placebo. What's more, the mRNA version of core-g28v2 60mer was able to neutralize HIV-like "pseudoviruses" that were missing a sugar molecule (N276 glycan) that hides the CD4 binding site.

A Phase I clinical trial (IAVI G002; NCT05001373) of the eOD-GT8 60mer primer (which Moderna calls mRNA-1644) and the mRNA core-g28v2 60mer booster (a.k.a. mRNA-1644v2-core) is currently underway.

Two other papers, published in Science, described the development of a different immunogen, dubbed N332-GT5, designed to elicit the production of another bnAb called BG18. Prior HIV prevention and treatment studies have shown than combining different bnAbs can help prevent viral escape.

One research team showed that the N332-GT5 primer vaccine activated BG18 precursor B cells in

all eight vaccinated macaque monkeys. The second team showed that adding one of two new booster immunogens (B11 and B16)—especially if delivered via mRNA—drove further maturation of these precursor cells in mice, leading to increased affinity for naturally occurring HIV.

MPER Vaccine

Meanwhile, researchers at the Duke Human Vaccine Institute reported on another vaccine candidate that targets a usually hidden part of HIV's envelope that remains stable as the virus mutates. As HIV's envelope proteins break apart in preparation for cell entry, the gp41 membrane proximal external region (MPER) is briefly exposed.

The HIV Vaccine Trials Network's HVTN 133 trial (NCT03934541) evaluated an engineered immunogen consisting of peptides in a lipid nanoparticle designed to train B cells to generate bnAbs that recognize and block MPER.

At last year's International AIDS Society Conference on HIV Science, Wilton Williams, PhD, reported that while most study participants had good immune responses, one person developed an anaphylactic reaction to the polyethylene glycol (PEG) in the vaccine. The study was stopped, and the researchers plan to substitute a PEG-free formulation. Williams and colleagues further described the findings in Cell.

The trial enrolled 20 healthy HIV-negative volunteers. At the time it was halted, 15 had received two of the four planned vaccine doses, and five had received three doses. Although germline targeting can be a slow process, nearly all participants had serum binding antibody and CD4 T-cell responses, and a majority had specific binding antibody responses to the MPER peptides targeted by the vaccine, after just two immunizations.

"To get a broadly neutralizing antibody, a series of events needs to happen, and it typically takes several years post-infection," Williams said in a Duke news release. "The challenge has always been to recreate the necessary events in a shorter space of time using a vaccine. It was very exciting to see that, with this vaccine molecule, we could actually get neutralizing antibodies to emerge within weeks."

Immunization induced polyclonal B-cell lineages of mature bnAbs and their precursors. After the second vaccine dose, the most potent bnAbs neutralized 15% of global tier 2 HIV strains (virus that is harder to neutralize) and 35% of clade B strains (the most common HIV subtype in North America and Europe). Precursor B cells appeared to remain in a state of development, allowing them to evolve along with the virus. What's more, the vaccine selected for "improbable" mutations that enhanced neutralization. The researchers noted, however, that an effective vaccine would likely need to have multiple components that target different sites on the HIV envelope.

"This work is a major step forward as it shows the feasibility of inducing antibodies with immunizations that neutralize the most difficult strains of HIV," said senior author Barton Haynes, MD. "Our next steps are to induce more potent neutralizing antibodies against other sites on HIV

to prevent virus escape. We are not there yet, but the way forward is now much clearer."

Moving Forward

While these findings are promising, they are early steps in a long process. Researchers have not yet tested whether the new vaccines protect animals exposed to HIV or its simian cousin SIV, much less whether they can prevent HIV acquisition at the population level. What's more, vaccine trials have gotten more difficult to conduct now that highly effective pre-exposure prophylaxis (PrEP) is widely available. Add to this the fact that vaccine regimens that require multiple doses delivered over time are unlikely to be feasible in the real world.

While a widely accessible HIV prevention vaccine is a high bar, these approaches might play another role: A therapeutic vaccine that generates bnAbs could potentially help bring about long-term remission—a functional cure—in people living with HIV. "[I]f we get it to work well enough, we could also give the vaccine to people on ART [antiretroviral therapy], which might eventually allow them to go off ART," Schief previously told POZ.

In addition, this sophisticated vaccine research may pay dividends far beyond the HIV field.

"Although HIV-1 vaccine researchers have not yet succeeded in their goals, technical developments in this field have consistently had wider influences—not least in the rapid development of the COVID-19 vaccines, which were based on delivery platforms and/or protein stabilization methods used in the HIV-1 vaccine field," Rogier Sanders, PhD, of Amsterdam University Medical Center, and John Moore, PhD, of Weill Cornell Medicine, wrote in a Perspective accompanying the Science reports. These studies "exemplify progress in the rational design of germline-targeting HIV-1 vaccines, and what is being learned will guide germline-targeting programs for inducing bnAbs against other human pathogens such as coronaviruses and influenza and hepatitis C viruses."

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