



Broadly Neutralizing Antibodies for HIV Prevention

Broadly neutralizing antibodies (bNAbs for short) represent a relatively new approach being tested for both the prevention and treatment of HIV infection.

Antibodies are naturally produced by B cells, a type of white blood cell that is a member of the complex family of cells that make up the immune system. Over the past decade, technologies have become available that can identify rare B cells capable of producing antibodies with strong anti-HIV activity against a broad array of virus variants, and these antibodies have been named bNAbs.

In most people with HIV, the antibodies generated in response to the virus are ineffective in blocking viral replication (sometimes referred to as “non-neutralizing” antibodies). These antibodies are detectable by the tests used to diagnose HIV, with the results described as “antibody positive” or “HIV positive.”

The reason these regular antibodies don't inhibit HIV is because the virus has evolved mechanisms to fend off certain antibody attacks. In particular, the outer envelope of HIV is a rapidly mutating, shape-shifting target covered in sugar molecules that prevent most antibodies from being able to stick to the virus.

However, research pioneered by IAVI and the Vaccine Research Center at the US National Institutes of Health has shown that some people with HIV do eventually generate bNAbs. These bNAbs are typically present at levels too low to benefit the individual, but they can be copied and manufactured for preventive or therapeutic administration at higher doses.

This research has led to the development of an ever-growing family of bNAbs with an alphabet soup of different codenames (see information from AVAC and TAG on the current bNAb pipeline).

One of the first bNAbs to be identified, VRC01, has been tested for HIV prevention in two large trials (the Antibody Mediated Prevention, or AMP, trials). The studies were a collaborative effort between the HIV

Vaccine Trials Network (HVTN) and HIV Prevention Trials Network (HPTN). VRC01 was administered by intravenous infusion every eight weeks. One trial recruited cisgender men and transgender men and women who have sex with cisgender men, the other cisgender women.

The AMP trials demonstrated that VRC01 was safe and that it was effective at blocking HIV acquisition among a subset of trial participants exposed to viruses that were susceptible to inhibition by the antibody (HIV incidence was reduced by an estimated 75% in this group). About 30% of the HIV strains circulating in communities where the study took place were susceptible to VRC01, but it was not able to block the remaining 70% of circulating strains. The high prevalence of HIV strains resistant to VRC01 meant that the antibody did not reduce the risk of HIV acquisition in the trial population overall.

Researchers believe the results of the AMP trials represent proof of concept that bNAbs can prevent HIV infection, but more potent and broadly active bNAbs will be needed in order for the approach to be more effective.

Since VRC01 was discovered, bNAbs with stronger activity against a broader range of HIV variants have been identified, and many are already under evaluation in clinical trials. Combinations of different bNAbs are also being studied. The hope is that combinations can address the problem of HIV resistance, similar to how triple-combination antiretroviral therapies were able to work for treatment after single and dual approaches failed to show durable benefit.

To ease the administration of combination bNAbs, researchers are designing single antibodies that are able to target multiple different parts of HIV at once—these are called bispecific or trispecific antibodies.

Because delivery by intravenous infusion is not ideal, studies are also looking at subcutaneous administration and modified long-acting version of bNAbs that might allow for less frequent dosing (e.g.,

every three or six months). While still at an early stage, some studies are investigating whether virus vectors adapted from gene therapy can be used for long-term delivery of bNAbs. These are harmless viruses that can potentially take up residence in muscle tissue and act as a factory for bNAb production.

The ultimate goal for scientists is to design HIV vaccines that can trigger production of bNAbs. Achieving this goal would allow people to produce their own bNAbs, so that scientists no longer have to find ways to administer them. But it's a difficult challenge because the pathway that leads to bNAb production by B cells is long and complex. Work is ongoing, and there have been some recent indications of progress, at least in terms of taking the first step down the path toward bNAb production.

AUGUST 2021

Made for the *We The People Research Cohort*

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