

One way that vaccines work is by prompting the immune system to create antibodies against a particular pathogen. Passive immunization, on the other hand, refers to the transfer of pre-made antibodies to a person. It is also sometimes referred to as antibody mediated prevention (AMP). Protection with transferred antibodies can occur naturally, such as when maternal antibodies are transferred to the fetus through the placenta, as well as artificially, when specific antibodies are administered (e.g., through infusion) to a person.

Researchers have been studying passive immunization for HIV prevention for a number of years. In past years, researchers have begun clinical studies of safety and tolerability with a number of bNAbs (3BNC117, PG9, VRC01) in HIV-positive and -negative individuals. A larger phase 2b prevention trial of VRC01 called the **AMP Study** began enrolling participants in April 2016, and studies of other bNAbs for both treatment and prevention are planned. Key issues include evaluating safety and tolerability of different doses, seeing what levels are required for efficacy and, hopefully, establishing proof of concept. From there, scientists can work to enhance bNAbs' breadth and potency and seek innovative ways to use this potential development for treatment and prevention.

GLOSSARY

Broadly neutralizing antibody (bNAbs):

Y-shaped protein produced by B cells (immune cells) that binds to a specific part of HIV's surface, rendering it harmless; bNAbs neutralize many different types of HIV in lab tests.

Half-life: The time required for half the amount of a substance to be eliminated from the body or to be converted to another substance.

HIV subtypes: Families of HIV viruses that have similar genetic sequences. A way of describing the diversity of the virus. Different subtypes, also referred to as clades, are found in different parts of the world.

Monoclonal antibody: Antibody made using identical immune cells that are all clones of the same parent cell.

Potency: Relationship between the therapeutic effect of a drug or vaccine and the dose necessary to achieve that effect.

Passive immunization: Transfer of antibodies to an individual (versus immunization with a vaccine that teaches the body to make the antibody itself).

PASSIVE IMMUNIZATION RESEARCH

An important piece of the puzzle

Early in the research process scientists knew that developing an HIV vaccine would be more challenging than many other vaccines. HIV mutates rapidly, allowing it to evade immune responses, and targets a key set of cells a vaccine is designed to produce. It has been hard to identify how a person's immune system would naturally protect against HIV infection—an important building block in vaccine design.

In the early 2000s, researchers started testing **passive immunization** with anti-HIV antibodies in animals to better understand its potential in protecting against HIV. They found that direct infusion of certain antibodies could prevent infection with strains of the virus that matched the antibody being tested. It is understood, though, that an antibody that only protects against one **HIV subtype** would not be widely effective given HIV's broad genetic diversity.

Since 2009, scientists have identified many new **broadly neutralizing antibodies (bNAbs)** that are effective in the lab at blocking HIV infection against a wide range of **HIV subtypes**. These antibodies have been selected for testing in HIV prevention, treatment and cure studies. In animal studies antibody levels declined over time, so repeat dosing was required to maintain a protective effect. Passive immunization clinical trials are now well underway, and additional research is ongoing to try and improve the **potency** and **half-life** of existing bNAbs. The hope is that more potent candidates will require smaller and less frequent dosing and still be safe and effective.

In 2015, preliminary results from a subset of small-scale clinical trials showed that passive immunization can reduce viral load in people living with HIV not on ART. Studies also show that the antibodies are safe and generally well-tolerated. Larger-scale studies to evaluate safety and efficacy of various bNAbs and dosing strategies for *both* treatment and prevention are planned.

If the current AMP Study provides proof of concept, (i.e., they show that bNAbs can be effective in reducing viral load and/or preventing infection), it could lead to additional passive immunization trials, as well as research on vaccines to help the body make these protective antibodies on its own.

Early 2000's

KEY QUESTION

Can passive infusion of antibodies protect against HIV infection in animals?

2009 - 2015

KEY QUESTION

What should the passive immunization clinical trials pathway look like?

KEY QUESTION

Which antibodies used in passive immunization could provide the most potent and long-lasting protection?

KEY QUESTION

How might this work contribute to the development of preventive HIV vaccines?

2016 and beyond

KEY QUESTION

Is real-world delivery of passive immunization possible?