Broadly Neutralizing Antibodies Delay HIV Rebound

A combination of two antibodies, dubbed 3BNC117 and 10-1074, maintained viral suppression for a year in two people.

April 27, 2022 By Liz Highleyman

A combination of two broadly neutralizing antibodies (bnAbs) led to prolonged viral suppression after stopping HIV treatment, according to a study presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2022) and recently published in Nature. While this study was small, the findings suggest bnAbs could one day be a component of a combination HIV cure strategy.

While the past decade has seen some progress towards a functional cure for HIV—meaning sustained viral remission without antiretroviral therapy (ART)—the field has been beset by disappointments. Antiretrovirals can keep HIV replication suppressed as long as treatment continues, but the virus inserts its genetic blueprints into the DNA of human cells and establishes a latent reservoir that is unreachable by antiretrovirals and invisible to the immune system. These so-called HIV proviruses can lie dormant in resting immune cells indefinitely while on treatment, but they usually start churning out new virus soon after antiretrovirals are stopped, making HIV very difficult to cure.

One approach to long-term remission is helping the immune system fight HIV. People with HIV do produce antibodies against the virus, but HIV mutates rapidly and is usually able to escape them. However, some people produce broadly neutralizing antibodies that target parts of the virus that don't change much. In previous studies, a combination of two such bnAbs, 3BNC117 and 10-1074, led to extended remission in monkeys and delayed viral rebound in people who stopped antiretrovirals.

Still in disbelief but our paper is now out in @nature!

We show that immunotherapy with two broadly

neutralizing anti-HIV-1 antibodies maintains virologic suppression for several months in people living with HIV in the absence of anti-retroviral therapy.https://t.co/eVem5yDE0C

— Christian Gaebler (@c_gaebler) April 14, 2022

Christian Gaebler, MD, and Michel Nussenzweig, MD, of the Laboratory of Molecular Immunology at the Rockefeller University, and colleagues conducted a study to test the two antibodies in people with chronic HIV infection who had been on suppressive antiretroviral therapy for at least a year. 3BNC117 and 10-1074 were developed at Rockefeller and have been licensed to Gilead Sciences.

The Phase Ib trial (NCT03526848) enrolled adults in New York City and Boston. They had been diagnosed with HIV for a median of 11.5 years and on suppressive ART for a median of 8.5 years. At baseline, they had an undetectable viral load and a CD4 count of at least 500. All but three were men, their ages ranged from 30 to 60 and the group was racially diverse. Those taking a non-nucleoside reverse transcriptase inhibitor were switched to an integrase inhibitor.

The 26 participants were randomized into two groups. Both groups received up to seven doses of 3BNC117 and 10-1074 (30 milligrams per kilogram of each) at two- to three-week intervals over 20 weeks. They were not screened to determine whether their particular strains of HIV were sensitivity to the antibodies, which has previously been shown to affect outcomes. Combining two antibodies with different targets can help overcome viral resistance.

In the first group, 18 people were randomly assigned to discontinue antiretroviral therapy two days after the first antibody infusions while a second group of eight people did so at week 26, after receiving all antibody doses. Viral load and CD4 count were monitored weekly, and ART was resumed if they experienced viral rebound (two consecutive viral load measurements over 200 copies through week 26 or over 1,000 copies during the latter part of the study), a declining CD4 count or symptoms of acute retroviral syndrome. Participants were counseled about the need to prevent HIV transmission during ART interruption in case their viral load rose.

Follow-up continued for 48 weeks after the first antibody infusions. Some participants withdrew from the study, did not receive the antibodies or did not undergo ART interruption because of disruptions related to COVID-19.

The antibody infusions were generally safe and well tolerated, and there were no serious adverse events. Of the 17 people in the first group who received the antibodies, 13 (76%) maintained viral suppression for at least 20 weeks after stopping antiretrovirals. CD4 counts did not change, nor

were there significant changes in activation markers on CD4 or CD8 T cells.

The overall median time to viral rebound in the first group was 28.5 weeks—significantly longer than the delayed rebound previously seen in an earlier study that used three antibody infusions over six weeks. Among those who received all seven antibody doses, the median time to viral rebound was 32 weeks, or 12 weeks after the last infusion. However, among people in the second group, who didn't stop ART until several weeks after the last antibody infusion, the median time to viral rebound was just seven weeks.

Participants who maintained viral suppression for more than 20 weeks experienced viral rebound after blood levels of one of the antibodies fell to a low level. But two people (12%) who received all seven antibody doses still maintained viral suppression after one year.

The researchers were not able to find any factors that predicted the time to viral rebound. An analysis of viral reservoirs performed six months after antibody administration showed a decrease in the number of intact proviruses (those capable of producing new virus), but there was no decline in the defective proviral reservoir (proviruses that don't produce new virus).

"These data suggest that antibody administration affects the HIV-1 reservoir, but additional larger and longer studies will be required to define the precise effect of antibody immunotherapy on the reservoir," the study authors concluded.

The researchers hypothesized that antibodies might alter the viral reservoir by targeting dividing cells that express HIV proteins or by enhancing CD8 T-cell immunity. They noted that a key challenge in antibody therapy is that available antibody combinations do not cover 100% of all HIV strains, and antibody sensitivity testing remains suboptimal.

"Despite these current challenges," they wrote, "long-acting antibodies may become a viable therapeutic option in combination with long-acting ART to achieve higher rates of sustained viral suppression among sub-populations of people living with HIV who face challenges with daily regimens."

These findings show that while broadly neutralizing antibodies can play a role in HIV remission, they do not work for everyone and their activity is temporary. This suggests they may be most useful as part of a combination cure strategy. The benefits of bnAbs may be greater if used by people with acute (new) HIV infection, before viral reservoirs are fully established, and they may be more effective in children. Broadly neutralizing antibodies are also being studied for HIV prevention.

Click here to read the study abstract.
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