Broadly Neutralizing Antibody Leads to Long-Term HIV Remission

One person treated with a broadly neutralizing antibody plus romidepsin remained in remission for 3.7 years.

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One individual treated with the broadly neutralizing antibody 3BNC117 plus the latency-reversing agent romidepsin remains in remission nearly four years after stopping antiretroviral therapy, according to study results presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2022). He and other study participants who received the antibody showed enhanced HIV-specific CD8 T-cell responses.

Antiretroviral therapy (ART) can keep HIV replication suppressed as long as treatment continues, but the virus inserts its genetic blueprints into the DNA of human immune 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 CD4 cells indefinitely while on antiretrovirals, but they usually start churning out new virus soon after the drugs are stopped, making HIV very difficult to cure.

One approach to long-term remission is to help 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 (bnAbs) that target parts of the virus that don't change much. In another study presented at CROI, a combination of two such bnAbs, 3BNC117 and 10-1074, led to prolonged viral suppression after stopping antiretrovirals.

Most HIV cure researchers experts think that combination approaches using different types of therapy hold the most promise. The so-called shock-and-kill strategy, for example, uses latency-reversing agents to flush HIV out of hiding, making it susceptible to immune-based therapies such as bnAbs.

Ole Søgaard, MD, of Aarhus University in Denmark, and colleagues conducted the eClear trial (NCT03041012) to test 3BNC117 plus romidepsin, a latency-reversing agent that can reactivate silent HIV proviruses and may also hinder the establishment of the proviral reservoir.

"In addition to their direct antiviral effect, bnAbs against HIV-1 may have a vaccinal effect by stimulating T-cell-specific immunity via immune complex formation, leading to dendritic cell

activation and enhanced antigen processing and presentation," the researchers noted as background.

The trial enrolled 59 participants in Denmark and London, mostly white men, who were starting HIV treatment for the first time. About half had acquired the virus within the past six months while the rest had chronic HIV. Prior research has shown that the viral reservoir is established soon after infection.

The participants were randomly assigned to receive antiretroviral therapy alone; antiretrovirals plus 3BNC117 administered at days 7 and 21 after ART initiation; antiretrovirals plus romidepsin administered at days 10, 17 and 24 after ART initiation; or a combination of ART, 3BNC117 and romidepsin. (Although five women were enrolled, none were randomized to the two 3BNC117 arms.) Pretreatment virus samples showed that about 60% of those in the 3BNC117 arms were fully sensitive to the antibody, meaning they had no evidence of pre-existing resistance.

After starting treatment, participants who received 3BNC117, romidepsin or both had a faster viral load decline compared to those who used ART alone. People who received 3BNC117 saw a greater decrease in infected cells that produce HIV RNA and the HIV p24 protein, indicating a greater reduction in the number of intact proviruses capable of replication. Those who were fully sensitive to 3BNC117 showed significantly greater HIV-specific CD8 T-cell responses at three months and 12 months.

After a year on their assigned therapies, the participants were given the option to stop their antiretrovirals in a closely monitored 12-week analytical treatment interruption; 20 agreed to do so. The study protocol called for participants to resume ART if their viral load rose above 5,000 copies or their CD4 count fell below 350.

Four of the five people whose HIV was fully sensitive to 3BNC117 maintained a viral load below 5,000 copies during the 12-week treatment interruption. In contrast, most people who either did not receive 3BNC117 or had pre-existing resistance to the antibody did not maintain such a low viral load after stopping ART. The addition of romidepsin did not appear to raise the likelihood of sustained viral remission. However, the researchers did note that people with high levels of interferon-gamma were more likely to remain in remission.

Most strikingly, one participant who received 3BNC117 and romidepsin still had a viral load below 50 copies at the end of the planned 12-week interruption and stayed off antiretrovirals. At the time of the report, he had maintained viral suppression for 3.7 years. What's more, HIV DNA measurements indicate that his viral reservoir continues to shrink, Søgaard said.

"3BNC117 during ART initiation led to faster second phase viral load decay and facilitate elimination of infected cells," the researchers concluded. "Interventions targeting the viral reservoir at ART initiation may alter the course of HIV infection," the researchers concluded.

The researchers are not calling this outcome a cure, as the man still has an extremely low blood viral load and residual HIV in his cells, so he could experience viral rebound with longer

observation. But the findings do suggest that broadly neutralizing antibodies such as 3BNC117 could become a component of a combination strategy for a functional cure.

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