Immune Modulator Anktiva Does Not Control HIV Rebound

The drug did have an effect on the viral reservoir and immune responses, suggesting it might play a role in a combination cure strategy.

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Most people with HIV who received the immune-modulating drug Anktiva (N-803), with or without broadly neutralizing antibodies, did not experience delayed viral rebound after stopping antiretroviral treatment, but they did show some favorable changes in immune response and the viral reservoir, according to a set of posters presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2026) in Denver.

These results—which conflict with findings reported at a conference last year—add to the growing evidence that a combination approach will be needed for a functional cure, or long-term remission without antiretrovirals.

Antiretroviral therapy can keep HIV suppressed indefinitely, but the virus inserts its genetic blueprints (known as a provirus) into CD4 T cells and establishes a long-lasting viral reservoir that is nearly impossible to eradicate. Cure researchers have tried many different strategies to control the virus, shrink the reservoir and boost immune response, but so far progress has been modest.

Anktiva, from ImmunityBio, is an interleukin 15 (IL-15) receptor superagonist that activates natural killer cells and CD8 killer T cells and enhances CD4 helper T-cell activity and proliferation of memory T cells. The Food and Drug Administration approved Anktiva as a treatment for bladder cancer in 2024, and Saudi Arabia recently approved it for advanced lung cancer. It is currently being studied for several other malignancies, often in combination with immune checkpoint inhibitors, in an effort to strengthen immune responses against tumors. Early research suggests Anktiva may also help the immune system fight HIV and might reactivate latent virus in the reservoir.

Three clinical trials—ACTG A5386 (NCT04340596), a study sponsored by Rockefeller University (NCT05245292) and the Thai RV550 study—assessed whether Anktiva, with or without broadly neutralizing antibodies (bnAbs), could delay viral rebound after antiretroviral treatment interruption and boost immune response against HIV. Therapeutic bnAbs are manufactured versions of specialized antibodies that target conserved parts of the virus.

At last summer's International AIDS Society Conference on HIV Science, researchers presented initial findings from the Rockefeller trial, which tested Anktiva plus two bnAbs, 3BNC117-LS and 10-1074-LS. That study enrolled 28 people with chronic HIV infection on stable antiretroviral therapy with a sustained undetectable viral load. They received a single IV infusion of the bnAbs, followed by up to eight injections of Anktiva three weeks apart. Two days after bnAb administration, they started a closely monitored analytical treatment interruption (ATI).

Four people resumed their antiretrovirals before viral rebound occurred, and 10 experienced early viral rebound as expected after stopping treatment. But of the 24 people who did not restart treatment prior to rebound, 58% remained off antiretrovirals at 24 weeks, 29% were still off at 48 weeks and three (13%) did not need to resume treatment even at 72 weeks, including one who remained off antiretrovirals for 125 weeks at the time of the report.

ACTG A5386

At CROI, however, researchers with the other two trials did not report such encouraging results.

Brad Jones, PhD, from Weill Cornell Medicine, and colleagues presented findings from the Phase I ACTG A5386, sponsored by the National Institutes of Allergy and Infectious Diseases. This study included 48 adults with chronic HIV infection who were on antiretroviral therapy with viral suppression for more than 96 weeks. Most (90%) were men, and the median age was 50 years. They were tested for sensitivity to two bnAbs, VRC07-523-LS and 10-1074-LS. The 23 participants whose HIV was sensitive to one or both bnAbs received them along with Anktiva, while 25 people who were not sensitive received only Anktiva.

The bnAbs were administered at the start of the study, followed by up to eight doses of Anktiva given three weeks apart. Both therapies were generally safe and well tolerated, but eight people developed severe neutropenia (white blood cell deficiency) thought to be possibly attributable to Anktiva.

In contrast to the Rockefeller study, which started a treatment interruption two days after bnAb administration, ACTG A5386 participants stayed on their antiretrovirals while receiving the bnAbs and Anktiva. Nineteen people who got both the bnAbs and Anktiva started a treatment interruption at 52 weeks. (This poster did not report ATI results for those who received only Anktiva.)

Of these 19, seven requested to restart their antiretrovirals and six experienced viral rebound (above 1,000 copies). Only one person (5%) met the primary endpoint with a viral load below 200 at eight weeks off antiretroviral therapy and three had a viral load below 1,000 at that timepoint. One participant restarted antiretrovirals at 24 weeks and one remains off treatment.

"N-803 plus bnAbs did not lead to viral control after [antiretroviral therapy] cessation as hypothesized," the researchers concluded. They are further investigating which factors might be associated with viral control in the two people with longer remission.

However, Anktiva did appear to have some effect on the viral reservoir and immune responses

against HIV. In an analysis of 42 people performed after five doses of Anktiva, 70% showed a transient decline in intact provirus HIV DNA (median –0.19 log with Anktiva alone; –0.25 log with Anktiva plus bnAbs). Intact reservoir levels rebounded to near baseline by 10 weeks after completion of dosing.

In a second analysis, Itzayana Miller, a PhD student at Weill Cornell, and colleagues looked at T-cell features associated with viral control in ACTG A5386. According to this poster, two people who received only Anktiva maintained a viral load below 1,000 for 24 weeks, in addition to those described by Jones who got both Anktiva and bnAbs.

Those who received Anktiva with or without bnAbs showed modest shifts toward "stem-like" T cells (TCF-1+ and stem cell memory CD8 cells) with a high capacity for proliferation, more potent activity against HIV and less evidence of exhaustion. This type of T cell has been previously linked to posttreatment control of HIV. What's more, those with evidence of HIV control showed high proliferation of Gag- and Nef-specific CD8 T cells and Gag- and Pol-specific CD4 T cells.

RV550

The Phase II RV550 trial, sponsored by the U.S. Military HIV Research Program and conducted by the Thai Red Cross, took a different approach, evaluating the effect of N-803, in combination with antiretrovirals, on the viral reservoir in people with acute HIV infection. People who start treatment very soon after acquiring HIV have a smaller reservoir and a better chance of achieving remission.

In step 1 of this study, 12 participants were randomly assigned to receive antiretrovirals therapy either alone or with three doses of Anktiva administered three weeks apart. In step 2, seven of them received a dose of Anktiva regardless of randomization and started an analytical treatment interruption.

The researchers previously reported that people who received antiretroviral therapy plus Anktiva experienced faster viral load decline than those on antiretrovirals alone, but there was no difference in HIV DNA levels in the blood. The study presented at CROI showed that with additional analysis of lymph nodes and other tissues, Anktiva recipients did show a substantial decrease in viral RNA. However, there were no significant differences between the two groups in time to viral rebound, peak viral load, time to treatment reinitiation or how long it took to resuppress the virus after resuming antiretrovirals.

"N-803 was safe but did not significantly alter viral rebound kinetics during ATI," the researchers concluded. "However, N-803 decreased viral RNA in lymph nodes by 50-fold and may be effective in future combinatorial strategies."

Taken together, these findings offer further evidence that combination approaches have the best prospects for inducing long-term HIV remission that could allow people to stay off antiretrovirals for several months or longer.

Anktiva might be a component of such functional cure strategies, but bispecific antibody-like constructs that deliver IL-15 directly to memory CD4 cells might hold even more promise. T4IL15 and T4IL15Δ, developed by David Ho, MD, and colleagues at the Aaron Diamond AIDS Research Center, demonstrated “an unprecedented propensity to activate latent HIV-1,” according to the researchers.

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