Cancer Immunotherapy Flushes HIV Out of Hiding

Keytruda can activate T cells that harbor latent HIV, a possible step toward a functional cure.

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A widely used cancer immunotherapy drug can flush latent HIV out of its hiding places and could potentially be used in combination with other types of therapy to achieve long-term remission, according to research published in Science Translational Medicine.

“Being able to stop HIV from hiding in cells is an important part of finding an HIV cure, and this signifies exciting progress,” said International AIDS Society president Adeeba Kamarulzaman, MBBS.

People with HIV and cancer who were treated with the anti-PD-1 checkpoint inhibitor Keytruda (pembrolizumab) saw an increase in their HIV viral load, suggesting that the drug activated resting T cells that contain HIV blueprints and reversed viral latency.

“We’re endeavoring to ascertain the effect anti-PD-1 has on the HIV-specific killer T cells in the hope that as well as reversing HIV latency, it will also rev up the immune system to kill the HIV-infected cells in the way it does with cancer,” senior study author Sharon Lewin, MD, of the Peter Doherty Institute for Infection and Immunity at the University of Melbourne in Australia, said in a press release.

1/Excited to see our results evaluating the effects of anti-PD1 mAB on HIV infected cells from a collaboration with @ProfSharonLewin and @DAREtoCureHIV published today! https://t.co/umLYefC1Zy

— Thomas Uldrick, MD (@ThomasUldrick) January 27, 2022

“Anti-PD-1 did not eradicate HIV in this study, but results inform efforts to manipulate T-cells to cure HIV,” lead author Thomas Uldrick, MD, of Regeneron (formerly with the Fred Hutchinson Cancer Research Center and the National Cancer Institute’s HIV and AIDS Malignancy Branch), said on Twitter.

The past decade has been marked by both progress and disappointments in the quest to achieve a functional cure for HIV, meaning sustained viral remission without antiretroviral therapy. While antiretrovirals can keep HIV replication suppressed as long as treatment continues, the virus inserts its genetic blueprints into the chromosomes of human cells and establishes a long-lasting latent reservoir that is invisible to the immune system and unreachable by antiretrovirals—a major barrier to a cure. These HIV proviruses can lie dormant in resting T cells indefinitely, but they usually start churning out new virus when treatment stops.

Several approaches have been explored in an effort to achieve long-term remission. The “shock and kill” strategy (also known as “poke and clear”) involves waking up dormant proviruses with latency-reversing drugs and flushing HIV out of hiding. Conversely, the “block and lock” approach aims to keep the latent virus in a deep sleep.

Lewin, Uldrick and colleagues evaluated the impact of the anti-PD-1 checkpoint inhibitor Keytruda on HIV latency in 32 people with HIV and cancer who were taking antiretroviral therapy. Keytruda was administered by IV infusion every three weeks.

PD-1 is a checkpoint receptor on T cells that plays a role in regulating immunity. Normally, its role is to dampen excessive immune responses, and it is expressed on “exhausted” T cells that no longer function properly. Some cancers can hijack PD-1 to turn off immune responses against them. PD-1 also suppresses CD8 killer T cells that target HIV. What’s more, PD-1 is heavily expressed on CD4 helper T cells that harbor hidden HIV, and it plays a role in maintaining viral latency.

Checkpoint inhibitors are monoclonal antibodies that block PD-1, releasing the brakes and restoring T-cell activity. Keytruda, the first approved anti-PD-1 inhibitor, is widely used to treat malignancies including breast cancer, colon cancer, lung cancer and melanoma.

After the first infusion of the monoclonal antibody, unspliced HIV RNA increased by a median of 1.32-fold, while the ratio of unspliced HIV RNA to HIV DNA in CD4 T cells in the blood rose by 1.61-fold. In addition, HIV RNA viral load in the blood plasma rose by 1.65-fold. After six cycles of Keytruda, study participants had more CD4 T cells that were capable of producing new virus. However, they did not have more total HIV-infected cells, according to Uldrick.

These data suggest that Keytruda can reverse HIV latency, making the virus visible to the immune system and susceptible to antiretrovirals. This supports the rationale for combining PD-1 checkpoint inhibitors with other interventions to reduce the HIV reservoir, the researchers concluded.

But unleashing T cells with checkpoint inhibitors can lead to side effects, including excessive

inflammation that can harm organs throughout the body. This could limit the use of this strategy for HIV-positive people who do not have cancer and are doing well on antiretroviral therapy. Lewin's team is starting a study to evaluate whether a low dose of Keytruda is safe for this population.

"It's not straightforward to bring this approach to the clinic in people living with HIV without cancer," Lewin explained. "The side effects of immunotherapy currently are significant, for example, 5% to 10% of people will get an adverse event. In a cancer setting this isn't a major concern as you have a life-threatening illness, but in HIV, the situation is very different. People can now live normal and healthy lives with HIV, so any intervention for a cure must have very low toxicity."

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