Study finds cancer immunotherapy treatment can reverse HIV latency

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An international research collaboration has found the cancer immunotherapy treatment, pembrolizumab, can reverse HIV latency, the ability for the virus to 'hide' inside cells of people living with HIV on

antiretroviral therapy, the major barrier to a cure for HIV.

Pembrolizumab is a monoclonal antibody that reverses the 'exhaustion' of the immune system. Specifically, when killer T cells get worn out they express proteins on their surface, one of which is called PD1. The monoclonal antibodies, also referred to as anti-PD-1, work by blocking these exhaustion markers, allowing the killer T cells to regain function and kill the cancer. The drug has revolutionized the treatments of several cancers, including melanoma.

In the context of HIV, previous research conducted by Professor Sharon Lewin—Director of the Peter Doherty Institute for Infection and Immunity (Doherty Institute), a world leader in HIV cure research and co-lead of this latest clinical trial—and her team, found the PD1 exhaustion markers allow the virus to go into hiding.

Published in *Science Translational Medicine* today, this latest study is the largest, multicentre prospective clinical trial of pembrolizumab in people with cancer who are also living with HIV. Professor Sharon Lewin said that up until now, there had only been case reports to show the effect of anti-PD-1 because people with HIV who also need this treatment for their cancer are very rare.

"It's not straightforward to bring this approach to the clinic in people living with HIV without cancer," explained Professor Lewin.

"The side effects of immunotherapy currently are significant, for example, five to 10 percent 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.

"In this study, we were able to show that in a cohort of 32 people who have cancer who are also living with HIV, pembrolizumab was able to perturb the HIV reservoir, which is a very exciting result and involved many groups around the world."

The study enrolled participants in the US through the Cancer Immunotherapy Network, based at the Fred Hutchinson Cancer Research Center in Seattle, and the clinical trial was led by Professor Thomas Uldrick, a medical oncologist and expert in cancer immunotherapy.

"We were excited to team up with Professor Lewin and colleagues in DARE to leverage this important clinical trial for cancer in people with HIV to design a study to evaluate the effects of anti-PD-1 therapy on the underlying HIV in people who were on effective antiviral medicines for HIV," said Dr. Uldrick.

Blood from study participants was collected before and after treatment with pembrolizumab. The HIV virus was then interrogated by Professor Lewin's team at the Doherty Institute and by collaborators at the University of Montreal and the National Cancer Institute in Frederick, Maryland.

Professor Lewin said work would continue on the samples obtained from this study to now also understand how pembrolizumab modifies the immune response to HIV.

"It's an incredible opportunity because we know exactly what the T cells are responding to. We're endeavoring to ascertain the effect anti-PD-1has 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."

In addition, Professor Lewin and her team have a clinical trial approved to understand how anti-PD-1 works in people without cancer, which has been put on hold due to the COVID-19 pandemic.

"This study will look at the effects of anti-PD-1 in both the lymph nodes and the blood to try and find the lowest, safest dose."

More information: Pembrolizumab Induces HIV Latency Reversal in People Living with HIV and Cancer on Antiretroviral Therapy, *Science Translational Medicine* (2022). www.science.org/doi/10.1126/scitranslmed.abl3836

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