Research offers new insights into how immunotherapy could help treat or functionally cure HIV

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Immunotherapy has revolutionized treatment options in oncology, neurology, and many infectious diseases and now there is fresh hope that the same method could be used to treat or functionally cure HIV, according to two related studies from Perelman School of Medicine at the University of Pennsylvania, the University of Alabama at Birmingham (UAB), and the National Institutes of Health (NIH).

Published online today in the *New England Journal of Medicine*, the research offers new insights into how immunotherapy could be used to develop a functional cure for HIV and eliminate the need for people living with the virus to take a daily regimen of medications.

The study, which examined chronically HIV-infected participants, found that injections of one broadly neutralizing HIV antibody (bNAb), known as VRC01, were safe, generated high levels of the antibody, and modestly delayed the time of HIV viral rebound compared to historical controls. However, suppression did not surpass 8 weeks in the majority of participants. By demonstrating that HIV-specific antibodies could be successfully administered as long-acting agents to suppress or even kill HIV-infected cells, this method is a first step toward the ultimate goal of durable suppression of HIV in the absence of ART.

"I would compare these findings to early days of HIV treatment research in the late 1980s," said Pablo Tebas, MD, a senior author of the study and director of the AIDS Clinical Trials Unit at Penn. "In this study, we looked at one antibody, but we think it may take combinations of more potent antibodies to successfully control the virus."

In the early years of HIV drug development, the first antiretroviral medicines were used as single agents to treat people living with HIV. The virus quickly developed resistance and rebounded in the blood. As additional antiretroviral drugs were introduced to target various aspects of HIV, combination drugs led to more effective and prolonged viral suppression.

Currently, most people living with HIV take a once-daily combination of antiretroviral therapy (ART), which prolongs life expectancy and improves overall health, but cannot completely eradicate the virus. Adherence to a daily HIV medication continues to be a challenge for many people living with HIV, especially in resource-limited settings. However, the vast majority of people living with HIV experience rapid rebound if ART is stopped or interrupted, making those people sicker and more likely to spread the virus to others.

Through bNAb immunotherapy, people living with HIV could potentially receive an injection of antibodies or another immunological intervention that would suppress the virus. The injection would remove HIV from a person's blood and enable control of the virus without a daily ART regimen.

"For the near future, it is unlikely that we will be able to fully eradicate HIV once a person has been infected. But a functional cure is a reasonable intermediate goal," Tebas said.

A functional HIV cure means that while the virus would still exist in a person's body in extremely small amounts, virus replication would be durably suppressed, disease progression drastically slowed, and symptoms of infection stopped - all without the need for daily medications.

"The goal of immunotherapy is to eliminate the need to take a pill every single day while simultaneously chipping away at the latent reservoir of virus-infected cells. However, we are still years away from that goal. And even if a person is able to be functionally cured of HIV, long-term follow-up will be essential to ensure that the virus doesn't return to high levels," Tebas said.

The bNAb tested in this trial did not provide long-lasting virus control in participants. Investigators tested historical blood samples from trial participants that were stored at both Penn and UAB's Centers for AIDS Research (CFAR) in order to determine if there was pre-existing resistance to bNAb immunotherapy and reveal its limitations as a potential cure. They found that the trial participants with the shortest times of HIV suppression harbored viruses that were resistant to the bNAb.

"We found that many trial participants had HIV that was resistant to the bNAb immunotherapy long before they

entered the trial. This pre-existing resistance to HIV-targeting bNAbs was a barrier to effective immunotherapy here, and will continue to present challenges to HIV bNAb therapies moving forward," said Katharine Bar, MD, first author of the study and director of Viral and Molecular Core of the Penn Center for AIDS Research (CFAR).

Bar notes that this study was a collaborative effort between several institutions. "The close collaboration between the Penn and UAB CFARs with the AIDS Clinical Trials Group (ACTG) enabled us to characterize the pre-existing resistance and identify it as a key barrier to developing bNAb immunotherapy as an HIV cure. Continued collaboration between CFARs and the ACTG will be instrumental as we continue to move this research forward."

Future trials that are now in development will test whether combinations of more potent bNAbs can provide durable virus suppression and potentially reduce the size of the persistent reservoir.

Source:
University of Pennsylvania School of Medicine
