New trial highlights incremental progress towards a cure for HIV-1

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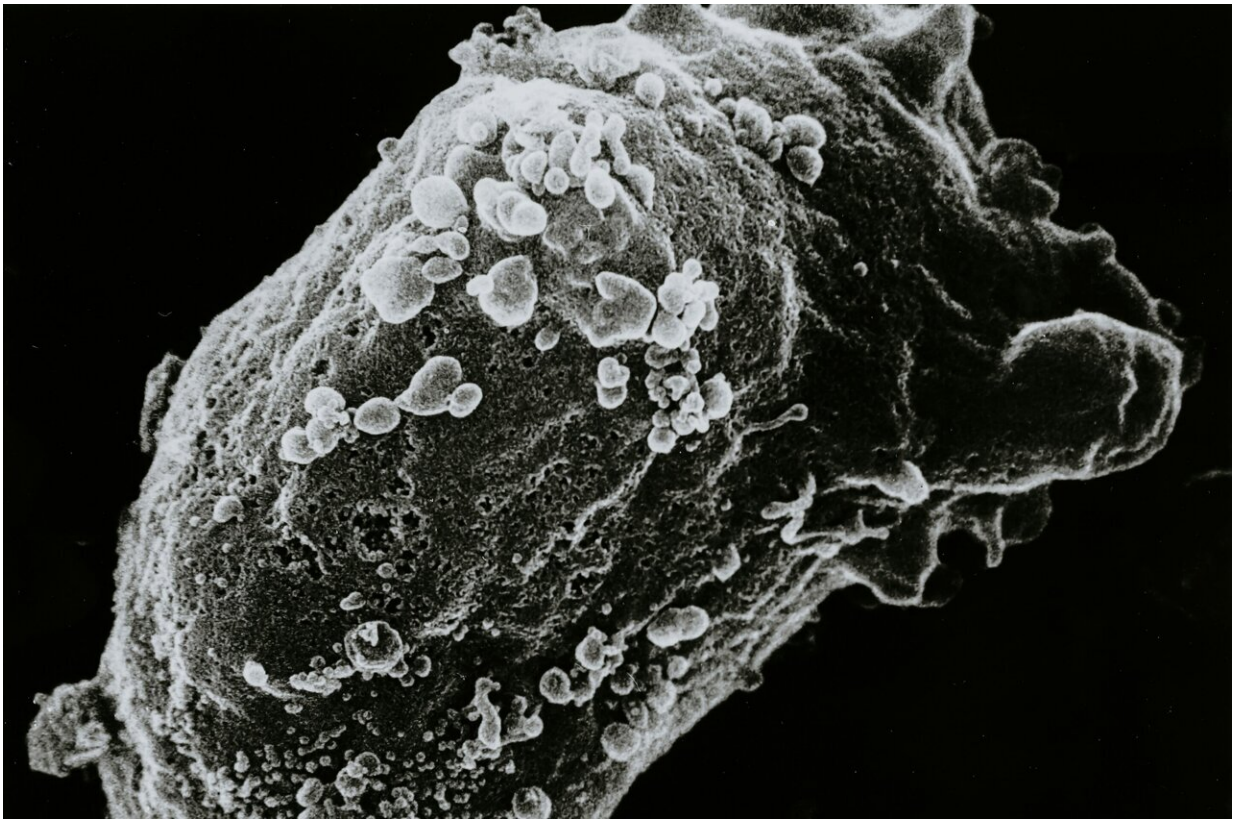

Lymphocyte with HIV cluster. Credit: Unsplash/CC0 Public Domain

Antiretroviral therapies (ART) stop HIV replication in its tracks, allowing people with HIV to live relatively normal lives. However, despite these treatments, some HIV still lingers inside cells in a dormant

state known as "latency." If ART is discontinued, HIV will awaken from its dormant state, begin to replicate, and cause acquired immunodeficiency syndrome (AIDS). To create a cure, researchers have been attempting to drive HIV out of latency and target it for destruction.

A new clinical trial led by Cynthia Gay, MD, MPH, associate professor of infectious diseases, David Margolis, MD, the Sarah Kenan Distinguished Professor of Medicine, Microbiology & Immunology, and Epidemiology, and other clinicians and researchers at the UNC School of Medicine suggests that a combination of the drug vorinostat and immunotherapy can coax HIV-infected cells out of latency and attack them.

The immunotherapy was provided by a team led by Catherine Bollard, MD, at George Washington University, who took white blood cells from the study participants and expanded them in the laboratory, augmenting the cells' ability to attack HIV-infected cells before re-infusion at UNC.

Their results, published in the *Journal of Infectious Diseases*, showed a small dent on the latent reservoir, demonstrating that there is more work to be done in the field.

"We did show that this approach can reduce the reservoir, but the reductions were not nearly large enough, and statistically speaking were what we call a 'trend' but not highly statistically significant," said David Margolis, MD, director of the HIV Cure Center and senior author on the paper. "We need to create better approaches to flush out the virus and attack it when it comes out. We need to keep chipping away at the reservoir until there's nothing there."

DNA inside cell nuclei is kept in a tightly packed space by chromosomes, which act as highly organized storage facilities. When you unfurl a chromosome, you'll find loop-de-loop-like fibers called

chromatin. If you keep unfurling, you'll see long strands of DNA wrapped around scaffold proteins known as histones, like beads on a string. Finally, when the unfurling is complete, you will see the iconic DNA double helix.

Vorinostat works by inhibiting a lock-like enzyme called histone deacetylase. By stopping this mechanism, tiny doors within the chromatin fibers unlock and open up, effectively "waking up" latent HIV from its slumber and making it vulnerable to an immune system attack. As a result, a tiny blip of HIV expression shows up on very sensitive molecular assays.

But the effects of vorinostat are short-lived, only lasting a day per dose. For this reason, Margolis and other researchers are trying to find safe and effective ways to administer the drug and keep the chromatin channels open for longer periods of time.

For the study, six participants were given multiple doses of vorinostat. Researchers then extracted immune cells from the participants and expanded the cells that knew how to attack HIV-infected cells.

This immunotherapy method, which has been successful against other viruses such as Epstein-Barr virus and cytomegalovirus, involves giving participants back their expanded immune cells in the hopes that these cells will further multiply in number and launch an all-out attack on the newly exposed HIV-infected cells.

However, in the first part of this study, only one of the six participants saw a drop in their HIV reservoir levels. To test whether the result was simply random or something more, researchers gave three participants their usual dose of vorinostat, but introduced five times the amount of engineered immune cells. All three of the participants had a slight decline in their reservoirs.

But, statistically speaking, the results were not large enough to be definitive.

"This is not the result we wanted, but it is research that needed to be done," said Margolis. "We are working on improving both latency reversal and clearance of infected cells, and we hope to do more studies as soon as we can, using newer and better approaches."

Many of the participants in the study have been working with Margolis's research team for years, sacrificing their own time and blood for research efforts. Their long-term partnership and commitment have been essential for data collection. The data, which follows the size of the viral reservoir in these people over years prior to this study, makes the small changes found more compelling.

"People living with HIV come in a couple of times a year, and we measure residual traces of virus in their blood cells, which doesn't have any immediate benefit to them," said Margolis. "It's a very altruistic action and we couldn't make any progress without their help."

More information: David M Margolis et al, The Effects of HIV-1 Antigen Expanded Specific T Cell (HXTC) Therapy and Vorinostat on Persistent HIV-1 Infection in People with HIV on Antiretroviral Therapy, *Journal of Infectious Diseases* (2023). DOI: 10.1093/infdis/jiad423

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