Clues to a Cure: Next Berlin Patient Has Powerful Natural Killer Cells

The man's highly efficient immune response may have helped eliminate residual HIV after a stem cell transplant.

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It's not yet clear how the 10 people cured of HIV after stem cell transplants have managed to eliminate the virus, as the cases have different factors that may have contributed to sustained remission without antiretrovirals. But new results presented at the European AIDS Conference in October (EACS 2025) suggest that in one case, unusually efficient natural killer (NK) cells may play a role.

Antiretroviral treatment can keep HIV suppressed indefinitely, but the virus inserts its genetic blueprints into host cells and establishes a long-lasting reservoir that is nearly impossible to eradicate. Only a small number of people have been cured of HIV after stem cell transplants for cancer treatment, starting with Timothy Ray Brown, the original Berlin Patient, in 2008.

At the 2024 International AIDS Conference, researchers presented the "Next Berlin Patient," a German man who appears to be cured after a stem cell transplant to treat acute myeloid leukemia, making him the seventh such case. The anonymous 60-year-old man was diagnosed with HIV in 2009 and received his transplant in October 2015. He stopped antiretroviral therapy in September 2018 and still has sustained HIV remission seven years later.

Researchers are still trying to figure out why these people were cured while some other HIV-positive people who received similar transplants weren't so fortunate.

Brown and six other people—the London Patient, the Düsseldorf Patient, the City of Hope Patient, the French Patient, the Chicago Patient and the Oslo Patient—were cured after receiving stem cells from homozygous donors with two copies of a rare mutation known as CCR5-delta32 that disables a receptor most strains of HIV use to enter cells. But the New York Patient received a combination of umbilical cord blood cells with the CCR5-delta32 mutation and adult stem cells without the mutation, the Next Berlin Patient received cells from a heterozygous donor with only one copy and the Geneva Patient received wild-type stem cells without the mutation.

These patients received different conditioning regimens with chemotherapy and, in some cases, radiation prior to their transplants, and they had varying severity of graft-versus-host disease,

which occurs when donor immune cells attack the recipient's body. The Geneva Patient also used ruxolitinib (Jakafi), an immune-modulating drug that may help shrink the HIV viral reservoir. Some experts think the size of the pre-existing reservoir may make a posttransplant cure more likely.

"It's not all about CCR5-delta32," HIV cure expert Sharon Lewin, MD, PhD, of the Peter Doherty Institute at the University of Melbourne, said at a media briefing about the Next Berlin Patient case. It's likely that "multiple factors play a role in remission," and these may differ from patient to patient.

Potent NK Cells

Looking for further clues, PhD student Timo Trenkner, of University Medical Center Hamburg-Eppendorf, and colleagues conducted a detailed analysis of the Next Berlin Patient's immune response after his stem cell transplant.

As reported in 2024, the man is CCR5-delta32 heterozygous, meaning he had one copy of the mutation and was therefore partially resistant to HIV before transplantation. His viral load was low, and he delayed starting antiretrovirals for several years after diagnosis. His CD4 T-cell count declined during this period, however, indicating that the virus was replicating and damaging his immune system, so he was not an elite controller. After the transplant, his plasma viral load remained suppressed, he had no detectable HIV DNA in peripheral blood cells and gut biopsies tested negative for the virus. The researchers could not induce virus production from his CD4 cells in the lab. No HIV-specific T-cell responses were detected, and his HIV antibodies were decreasing, suggesting there was no remaining virus to trigger an immune response.

In particular, Trenkner's team performed in-depth phenotyping and functional testing of the man's natural killer cells. While B cells and T cells are part of the adaptive immune system and target specific virus-infected or malignant cells, NK cells are part of the innate immune system and have more generalized, non-specific activity.

NK cells are increasingly studied in HIV cure research, as certain subsets have been linked to natural HIV control, enhanced antibody-dependent cellular cytotoxicity (ADCC) and reduced viral reservoirs, the researchers noted. Elite controllers, who naturally control the virus without antiretrovirals, often display higher HIV-specific ADCC activity, and the only moderately successful HIV vaccine trial (RV144) identified ADCC as a correlate of protection.

The man's peripheral blood mononuclear cells were genotyped for killer-immunoglobulin-like receptor genes, and his NK cells were analyzed using flow cytometry and standardized ADCC assays against rituximab-coated target cells, which carry a protein that marks them for destruction by the immune system. HIV-specific ADCC capacity was tested in plasma samples over time using an assay that shows activity against HIV's Env protein. This was compared with plasma from five elite controllers and broadly neutralizing antibodies (bnAbs) that are being evaluated for HIV prevention and treatment.

The man had a markedly higher frequency of a specific subset of NK cells (NKG2A+ CD57+) compared with HIV-negative people, people who tested positive for cytomegalovirus and other stem cell transplant recipients. NKG2A is an immune checkpoint that regulates immune cell activity. CD57 is expressed on mature NK cells that no longer proliferate but have potent cell-killing ability.

These NK cells did not show characteristics of adaptive immunity, but they nonetheless contributed to ADCC activity when they encountered target cells. Plasma collected around the time of the transplant showed high HIV-specific ADCC activity, exceeding that of elite controllers, which declined steeply a few years after transplantation. The man produced highly potent antibodies—more potent than the bnAbs—that efficiently targeted his strain of HIV.

“These data—together with findings from the first case of HIV-1 remission after transplantation with wild-type CCR5 donor cells (the Geneva Case)—suggest a potential contribution of NK cell-mediated mechanisms to modulate the HIV reservoir independent of CCR5-delta32 homozygosity,” the researchers concluded.

These findings suggest that therapies that promote NK cell activity might play a role in achieving a functional cure in people with HIV who do not receive stem cell transplants, which are too risky for those without life-threatening cancer. For example, other researchers reported this summer that one such therapy, Anktiva (N-803)—an interleukin 15 receptor “superagonist” that activates NK cells and CD8 killer T cells—may help delay or limit viral rebound in people treated with bnAbs.

“If we could induce the innate immune response to HIV seen in this patient in others, it would broaden our repertoire of approaches towards a possible cure,” said Michaela Müller-Trutwin, PhD, of the Pasteur Institute in Paris, who discussed the case findings at the conference.

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