The Next Berlin Patient: Another Man Cured of HIV After Stem Cell Transplant

This man received stem cells from a donor with just one copy of a mutation that makes T cells resistant to HIV.

July 18, 2024 By Liz Highleyman

[Editor's note: This case was presented at a July 18 press briefing in advance of the International AIDS Conference next week.]

A seventh person appears to be cured of HIV after a stem cell transplant for cancer treatment, according to a case study to be presented at the International AIDS Conference (#AIDS2024) next week in Munich. The man and his donor both have only a single copy of a rare mutation that prevents HIV from entering cells, raising questions about the keys to a functional cure.

The anonymous 60-year-old man was diagnosed with HIV in 2009 and received a transplant to treat acute myeloid leukemia in October 2015. He stopped antiretroviral therapy in September 2018 and still has sustained HIV remission nearly six years later, Christian Gaebler, MD, of Charité University of Medicine in Berlin told reporters.

The apparent success of this procedure suggests that the stem cell donor pool could be expanded, giving more HIV-positive cancer patients a chance to be cured of HIV. The procedure is too risky for people who don't have life-threatening malignancies, but each case offers new clues.

"All these cases are important scientifically—with every case, you learn more about what's possible and therefore what could be mimicked in an intervention," said International AIDS Society president and conference cochair Sharon Lewin, MD, PhD, of the Peter Doherty Institute at the University of Melbourne. While these cases are very rare, "they are inspirational to both people living with HIV and scientists," she added. "We need to give people hope but make it realistic."

A Handful of Cures—and Some Failures

Antiretroviral therapy 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.

To date, only a small number of people have been cured of HIV after stem cell transplants. The first, Timothy Ray Brown—the original Berlin Patient—received two transplants to treat acute myeloid leukemia in 2006. In the hope of curing both cancer and HIV, his oncologist, Gero Hütter, MD, from the same medical center in Berlin, had the idea to use stem cells from a donor with two matching copies—known as homozygous—of a mutation dubbed CCR5-delta32 that disables a receptor most strains of HIV use to enter cells.

Brown underwent intensive chemotherapy and whole-body radiation to prepare for the transplant. In effect, the conditioning regimen kills off existing malignant immune cells to make room for healthy new ones from the donor. Afterward, he developed near-fatal graft-versus-host disease, which occurs when donor immune cells attack the recipient. As first reported in 2008, he stopped antiretrovirals at the time of his initial transplant, but his viral load did not rebound. Over the years, researchers extensively tested his blood, gut and other tissues, finding no evidence of intact HIV anywhere in his body. At the time of his death in September 2020, he had been free of HIV for more than 13 years.

Three other people—Adam Castillejo (the London Patient), Marc Franke (the Düsseldorf Patient) and Paul Edmonds (the City of Hope Patient)—were also cured after receiving stem cell transplants to treat leukemia or lymphoma from donors with a double CCR5-delta32 mutation. They received less harsh conditioning chemotherapy and experienced milder graft-versus-host disease. All three remain off antiretroviral therapy without viral rebound, their cancer is still in remission and they will appear together at next week's conference.

Initially, experts assumed Brown's cure was attributable to the use of homozygous donor cells with a double CCR5-delta32 mutation. More than a decade ago, Timothy Henrich, MD, now at the University of California San Francisco, described two HIV-positive men in Boston who received transplants of stem cells without the mutation, known as wild-type. These cases generated much excitement as the patients appeared to control HIV after stopping antiretrovirals, but they ultimately experienced viral rebound three months and eight months after treatment interruption.

But Henrich's team later performed a mathematical modeling analysis that predicted a small number of transplant recipients would achieve a cure without CCR5-delta32 stem cells, he told POZ.

In early 2022, researchers described the New York Patient, a middle-aged, mixed-race woman with leukemia who received a combination of umbilical cord blood cells with the CCR5-delta32 mutation and partially matched adult stem cells from a relative without the mutation. Prior to the transplant, she received intensive chemotherapy and whole-body radiation, but she did not develop graft-versus-host disease. The CCR5-delta32 variation is most often found in people of Northern European descent, so this approach could potentially open up the procedure to more people of color. The woman stopped antiretrovirals three years after her transplant and at last report was still free of HIV.

The mystery deepened last year when researchers at the International AIDS Society Conference on

HIV Science presented the case of a man known as the Geneva Patient, who appears to have been cured after a wild-type stem cell transplant from a donor with no copies of the CCR5-delta32 mutation. This man received whole-body radiation and chemotherapy and experienced moderately severe graft-versus-host disease. He also used ruxolitinib (Jakafi), an immune-modulating drug that may help shrink the viral reservoir.

Another Berlin Patient

This brings us to the latest case—the new Berlin Patient—a man with a single copy of the CCR5-delta32 mutation, known as heterozygous. His doctors were unable to find a suitable donor with two copies of the mutation but found a heterozygous match with one copy. CCR5-delta32 heterozygous individuals can acquire HIV, but the disease generally progresses more slowly. About 16% of Northern Europeans have a single copy of the mutation, while only about 1% have two copies, Gaebler noted.

- Wild-type: no copies of CCR5-delta32
- Heterozygous: one copy of CCR5-delta32
- Homozygous: two copies of CCR5-delta32

Prior to the transplant, the man received whole-body radiation and intensive chemotherapy, and he developed mild graft-versus host disease. He achieved full chimerism, meaning all his immune cells eventually originated from the donor, and his leukemia went into remission.

The man discontinued antiretroviral treatment in 2018. Since then, his plasma viral load has remained suppressed, he has no detectable HIV DNA in peripheral blood cells and duodenal and ileum gut biopsies tested negative. 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 are decreasing, suggesting there may be no remaining virus to trigger an immune response.

The fact that the man received partially susceptible donor cells makes Gaebler more hesitant to declare that he's cured, but if he was going to experience viral rebound, it likely would have happened sooner than six years.

Researchers are still trying to figure out why these seven people were cured with stem cell transplants while other attempts have failed, but there does not seem to be a single decisive factor common to all cases.

Four of the men received transplants from CCR5-delta32 homozygous donors, one received cells from a heterozygous donor, one received wild-type stem cells and the woman received a mix of CCR5-delta32 homozygous and wild-type cells. Four patients underwent intensive conditioning therapy, while three received gentler regimens. Brown and the Geneva Patient experienced severe

graft-versus host disease, but the other did not.

Taken together, the seven cases suggest that “it’s not all about CCR5-delta32,” Lewin said. It’s likely that “multiple factors play a role in remission,” and these may differ from patient to patient. People who receive stem cells from CCR5-delta32 wild-type donors have the most susceptible T cells for the virus to target, people who receive stem cells from a heterozygous donor—or who are heterozygous themselves—have fewer vulnerable T cells and those with a homozygous donor have few or no susceptible cells. The size of the viral reservoir, the severity of graft-versus host disease and individual immune response are also important.

“We believe there was depletion of the replication-competent HIV reservoir, which cannot lead now to viral rebound,” Gaebler said. He thinks allogeneic immunity, or the immune response of the donor stem cells, might be key. Having one or two copies of the CCR5-delta32 mutation provides “an additional safety layer to give us protection with a resistant immune system,” but based on the new case and that of the Geneva Patient, “it is possible to cure HIV even when functional receptors for the virus are present. Maybe we do not fully need to achieve complete depletion.”

Henrich suggested that the conditioning regimen and graft-versus-host response may be key, while using CCR5-delta32 heterozygous donor cells leaves the virus with fewer targets. “This case demonstrates that by dramatically reducing the pretransplant HIV reservoir and maintaining this reduction over time with beneficial graft-versus-host effects, long-term remission remains a possibility for a small number of people even without CCR5-delta32 homozygous donor cells,” he told POZ.

Stem cell transplantation is an arduous procedure limited to people with advanced cancer, and it is far from a feasible solution for the vast majority of people living with HIV worldwide. But each new case provides clues that could lead to a more widely applicable functional cure. Some researchers, for example, are exploring whether gene-editing approaches such as CRISPR could be used to delete or disable CCR5 receptors to make an individual’s own immune cells resistant to HIV.

“The next Berlin Patient’s experience suggests that we can broaden the donor pool for these kinds of cases, although stem cell transplantation is only used in people who have another illness, such as leukemia,” Lewin said. “This is also promising for future HIV cure strategies based on gene therapy, because it suggests that we don’t have to eliminate every single piece of CCR5 to achieve remission.”

[This report has been updated to include comments from Timothy Henrich.]

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