New York Woman May Be Cured of HIV After Stem Cell Transplant

The woman's leukemia is in remission and she remains free of detectable HIV more than a year after stopping antiretroviral treatment.

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UPDATE: Details about this case were published in the March 16, 2023, issue of Cell.

A woman in New York City has no detectable HIV 14 months after stopping antiretroviral treatment and four and a half years after undergoing a new type of transplant using HIV-resistant stem cells, according to a presentation yesterday at the Conference on Retroviruses and Opportunistic Infections (CROI 2022).

The woman, who was being treated for leukemia, received a combination of umbilical cord blood cells with a rare mutation that blocks HIV entry and partially matched adult stem cells from a relative. She is doing well, and both her cancer and HIV are in remission. While it may be too soon to say for sure that she's cured, the New York Patient could join the Berlin Patient and the London Patient as the third person to be free of HIV after a stem cell transplant. But this is a risky procedure that will not be appropriate for most people living with the virus.

"This study provides hope for the use of cord blood cells or a combination of cord blood cells and haploidentical (half-matched) grafts to achieve HIV-1 remission for individuals requiring transplantation for other diseases," presenter Yvonne Bryson, MD, of the University of California at Los Angeles, said in a press release. "It also provides proof that HIV-1 viral reservoirs can be cleared sufficiently to afford remission and possibly cure in the setting of resistant target cells."

A New Type of Stem Cell Transplant

To date, only two people are widely regarded as being cured of HIV, although some others with a shorter duration of follow-up may eventually join their ranks.

The first, Timothy Ray Brown, known as the Berlin Patient, received two stem cell transplants to treat acute myeloid leukemia in 2006. The donor had two copies of a genetic mutation known as CCR5-delta32, which leads to an absence of CCR5 coreceptors, the gateways most types of HIV use to enter T cells. Brown underwent intensive conditioning chemotherapy and radiation to kill off his cancerous immune cells, allowing the donor stem cells to rebuild a new HIV-resistant immune

system. But the donor immune cells attacked his own cells, resulting in severe graft-versus-host disease.

Brown stopped antiretroviral treatment at the time of his first transplant, but his viral load did not rebound. Researchers extensively tested his blood, gut and other tissues, finding no evidence of replication-competent HIV anywhere in his body. At the time of his death in September 2020, due to a recurrence of his leukemia, Brown had been free of HIV for more than 13 years.

At CROI 2019, researchers reported that a second man, Adam Castillejo, dubbed the London Patient, had also achieved long-term HIV remission after a stem cell transplant, in this case to treat Hodgkin lymphoma. He, too, received cells from a donor with a double CCR5-delta32 mutation, but he underwent less aggressive pretransplant conditioning chemotherapy, was able to stay on antiretroviral treatment and had milder graft-versus-host disease. Again, extensive testing revealed no evidence of viable HIV. In September 2017, a year and a half after the transplant, he stopped antiretroviral therapy. He has been free of HIV for more than four years and his lymphoma is still in remission.

The latest case involves a middle-aged, mutiracial woman who was diagnosed with HIV in 2013 and acute myeloid leukemia in 2017. She's a participant in an observational study (IMPAACT P1107) that uses previously screened umbilical cord blood with a double CCR5-delta32 mutation. This mutation is present in only around 1% of people of Northern European descent and is even rarer in other populations. Being of mixed race, her chances of finding an adult donor who was both a close genetic match and carried the double mutation were very slim, especially since racial and ethnic minorities are underrepresented in most bone marrow donor registries.

Cord blood is more "forgiving" and does not require such an exact genetic match, but the amount of banked cells is too small for an adult transplant, and cord cells take longer to engraft, or become established in the body. So doctors at Weill Cornell Medical Center in New York performed a so-called haplo-cord transplant, which uses both CCR5-delta32 cord blood cells and partially matched adult donor stem cells without the mutation. The adult cells provide enough volume and faster engraftment, shoring up the immune system until the cord blood cells take over. Like Brown, the woman received intensive chemotherapy and whole-body radiation prior to the transplant.

The transplant went well, and the woman did not develop graft-versus-host disease, which is less common with cord blood. Within 100 days, she achieved full engraftment with 100% CCR5-delta32 immune cells derived from the cord blood. "She basically had a new HIV-resistant immune system," Bryson said. Laboratory tests showed that the new cells were resistant to HIV, and, surprisingly, they were even impervious to HIV strains that use a different coreceptor, known as CXCR4, instead of CCR5 to enter cells.

The woman remained on antiretroviral therapy for three years after the transplant. During this time, she had undetectable plasma viral load using the most sensitive tests, undetectable HIV DNA in immune cells (reflecting the viral reservoir) and no evidence of virus capable of replicating. Her

CD4 and CD8 T-cell counts fell after the conditioning regimen, as expected, but they rebounded and remained stable at around normal levels. What's more, she became HIV antibody negative a year after the transplant.

At that point, she decided to try a closely monitored antiretroviral treatment interruption. Fourteen months later, she has not experienced viral rebound, has undetectable HIV-specific cellular immune responses, is still HIV antibody negative and her leukemia remains in remission. Researchers have not been able to detect replication-competent HIV in nearly 75 million of her CD4 cells.

Clues to a Cure

Researchers are still exploring why these three apparent cures after stem cell transplantation were successful, while other attempts have failed. Using stem cells from donors with a double CCR5-delta32 mutation seems to be a key to success. At CROI 2012, researchers described two HIV-positive men in Boston who received stem cell transplants for cancer treatment from donors without the mutation. Although viral rebound was delayed, one man's HIV returned three months after stopping antiretrovirals, and the other man's rebounded eight months after treatment interruption.

Unlike Brown and the New York Patient, these men did not receive intensive conditioning therapy and radiation that could have wiped out existing immune cells that harbor HIV. But neither did Castillejo, and he nonetheless remains HIV-free. Some experts have suggested that the graft-versus-host reaction might have helped to keep HIV under control, but the New York woman did not experience this. So the secret to a successful posttransplant cure remains elusive.

Even if this mystery is solved, stem cell transplants are too dangerous for people who don't need them to treat life-threatening cancer. In addition, the procedure is medically intensive and expensive, and it would not be scalable to treat the millions of people living with HIV worldwide. In fact, Bryson estimated that only around 50 people with HIV might benefit from this approach in the United States. But the new case provides further clues that could lead to a more widely applicable approach to a cure.

"This third case of an HIV cure post–bone marrow transplant from a donor naturally resistant to HIV, and the first in a woman living with HIV, is a very exciting finding," said Sharon Lewin, president-elect of the International AIDS Society. "A bone marrow transplant is not a viable large-scale strategy for curing HIV, but it does present a proof of concept that HIV can be cured."

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