Geneva Man May Be Cured of HIV After Wild-Type Stem Cell Transplant

A new case raises questions about the keys to success for a functional cure after a stem cell transplant.

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Known only as the Geneva Patient, a sixth person appears to have been cured of HIV after a stem cell transplant for cancer treatment, according to a case study presented at the International AIDS Society Conference on HIV Science (#IAS2023) in Brisbane, Australia. But unlike the other five, this man received stem cells from a donor who does not have a rare mutation that prevents HIV from entering T cells.

The man received a transplant in July 2018 using so-called wild-type stem cells without the CCR5-delta32 mutation. He stopped antiretroviral treatment in November 2021 and has no evidence of HIV rebound or replicating virus 20 months later, Asier Sáez-Cirión, PhD, of Institut Pasteur in Paris, and Alexandra Calmy, MD, PhD, of Geneva University Hospitals, reported at a preconference press briefing.

“All the immunological markers we have analyzed have been unable to detect HIV products,” Sáez-Cirión said. “We cannot exclude that there is still some virus present…so there may be viral rebound in the future, although we hope this situation of viral remission remains permanent.”

Experts caution that continued monitoring and further testing are needed, as transplants using wild-type stem cells have failed to eliminate HIV in the past. The virus inserts its genetic blueprints into host cells and establishes a long-lasting viral reservoir that has proved nearly impossible to eradicate.

If stem cells with a double CCR5-delta32 mutation aren’t necessary, more HIV-positive cancer patients who need a transplant might have the chance to be cured of HIV as well. But the procedure is too risky for people who don’t have a life-threatening malignancy, and it is far from a feasible solution for the vast majority of people living with HIV worldwide.

“This is great news, and we know [cure news] always generates enormous interest from the media, but case reports are case reports,” said IAS president and conference cochair Sharon Lewin, MD, PhD, of the University of Melbourne.

Editor's note: Sáez-Cirión's full presentation will take place on July 24. POZ will update this report if additional information is provided.

The Geneva Patient

The latest case involves a white European man in his early fifties who was diagnosed with HIV in 1990 and was on continuous suppressive antiretroviral therapy (ART) since 2005. Despite being on effective treatment, he had residual detectable plasma HIV RNA and HIV DNA in CD4 T-cells,reflecting the viral reservoir, according to ultrasensitive tests before the transplant.

The man developed a rare and aggressive type of sarcoma and underwent chemotherapy and whole-body radiation before receiving an allogeneic stem cell transplant in July 2018. The unrelated donor did not have the CCR5-delta32 mutation, which knocks out receptors that most strains of HIV use to enter cells. No compatible donors with the mutation were available.

The man achieved full chimerism, meaning all his immune cells originated from the donor. He experienced acute and chronic graft-versus-host disease, which occurs when donor immune cells attack the recipient's body, and was treated with various immunosuppressive medications. Three years posttransplant, he and his doctors decided to try a treatment interruption in November 2021. After this, he used on-demand pre-exposure prophylaxis (PrEP) twice.

Now, 20 months after stopping antiretrovirals, the man still has viral suppression using standard tests, and ultrasensitive tests have become undetectable too. HIV DNA in his T cells and bone marrow decreased dramatically after the transplant—though it was sporadically detected early on—and the researchers could find only defective, not intact, virus. In laboratory studies, they could not induce virus production from the man's CD4 cells, and HIV DNA was undetectable in gut biopsies.

What's more, no HIV-specific T-cell responses were detected, and the man's HIV antibodies progressively declined, suggesting there may be no remaining virus left to trigger the immune system.

In short, the man "has no evidence of HIV-1 RNA rebound or replicating virus," the researchers concluded. "These results suggest that HIV remission could be achieved in some cases in the context of [allogeneic stem cell transplant] with wild-type CCR5."

A Handful of Cures—and Some Failures

So far, only a small number of people have been cured of HIV after stem cell transplants. The first, Timothy Ray Brown, known as the Berlin Patient, received two transplants to treat leukemia in 2006. His oncologist, Gero Hütter, MD, came up with the idea to use stem cells from a donor with the CCR5-delta32 mutation, speculating that it might cure both cancer and HIV.

Brown underwent intensive conditioning chemotherapy and whole-body radiation to prepare for the transplant. Afterward, he developed near-fatal graft-versus-host disease. 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.

The London Patient, Adam Castillejo, underwent a stem cell transplant in 2016 to treat lymphoma, also receiving cells from a donor with a double CCR5-delta32 mutation. But he received less aggressive conditioning chemotherapy than Brown and developed milder graft-versus-host disease. He stopped antiretroviral treatment a year and a half after his transplant, and he remains free of HIV. (POZ profiled Castillejo in June 2022.)

In early 2022, researchers described the New York Patient, a middle-aged, mixed-race woman with leukemia who in 2017 received a combination of umbilical cord blood cells with the CCR5-delta32 mutation and partially matched adult stem cells from a relative. She stopped antiretrovirals three years after her transplant; at last report she was still free of HIV.

Later that year, researchers announced that the City of Hope patient, a Southern California man who received an HIV-resistant stem cell transplant in early 2019 and stopped antiretrovirals two years later, remains in long-term remission. Because he is older, he received a less harsh conditioning chemotherapy regimen and developed only mild graft-versus-host disease. (Paul Edmonds revealed his identity in April.)

Finally, Marc Franke, long known as the Düsseldorf Patient, received a stem cell transplant from a donor with a double CCR5-delta32 mutation more than a decade ago and stopped ART nearly five years ago. He is still free of HIV, and earlier this year, his doctors finally declared that he's cured. (Franke described his experience in the July/August 2023 issue of POZ.)

Researchers are still trying to figure out why these people were cured after stem cell transplants, while other attempts have failed. Until now, many experts assumed that using stem cells from a donor with a double CCR5-delta32 mutation was the key to success. But the new case reopens questions about the role of conditioning therapy, the graft-versus-host reaction, immunosuppressive medications and natural killer cells.

A decade ago at the 2013 IAS Conference, Timothy Henrich, MD, now at the University of California San Francisco, described two HIV-positive men in Boston who received transplants to treat lymphoma using stem cells from donors without the CCR5-delta32 mutation.

These cases generated much excitement, as the patients appeared to be controlling HIV after stopping antiretrovirals. But hopes were dashed when the men ultimately experienced viral rebound, three months and eight months after treatment interruption. A few other cases of HIV remission after wild-type stem cell transplants have been reported, the longest lasting nine and a half months.

The Geneva patient "has already achieved far longer durable HIV remission without treatment than the Boston patients, lasting 20 months so far," said Lewin. "So this is promising, but we

learned from the Boston patients that even a single virion can lead to HIV rebound. This individual will need to be watched closely over the next months to years."

According to Henrich, this case raises several interesting possibilities, including the impact of the Geneva Patient's sporadic PrEP use.

"It is possible that in the setting of a very low reservoir with a very rare chance of viral reactivation events, intermittent ART exposure may have partially suppressed whatever low-level residual viral activity was smoldering in tissues, leading to longer-term remission," he speculated. The man's ongoing chronic graft-versus-host disease and long-term use of the JAK/STAT inhibitor ruxolitinib may have also contributed.

"This case is unique as it extends the interval prior to viral rebound for at least a year," Henrich told POZ. "Whatever the contribution of each of these factors, there is a suggestion that long-term remission following allogeneic stem cell transplant with CCR5 wild-type donor cells may be possible, but is likely to be rare."

While stem cell transplants remain limited to people with advanced cancer, 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 including zinc finger nucleases and CRISPR could be used to delete or disable CCR5 receptors to make an individual's own immune cells resistant to HIV.

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