

## Stem cell transplant does not cure SHIV/AIDS after irradiation of infected rhesus macaques

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Human immunodefieciency virus (HIV). Credit: C. Goldsmith/public domain

A study published on September 25th in *PLOS Pathogens* reports a new primate model to test treatments that might cure HIV/AIDS and suggests answers to questions raised by the "Berlin patient", the only human thought to have been cured so far.

Being HIV-positive and having developed leukemia, the Berlin patient underwent irradiation followed by a bone-marrow transplant from a donor with a mutation that abolishes the function of the CCR5 gene. The gene codes for a protein that facilitates HIV entry into <u>human cells</u>, and the mutation—in homozygous carriers who, like the donor, have two defective copies—protects against HIV infection.



Several factors could have contributed to the cure of HIV/AIDS in the patient: (1) the ablation of blood and immune <u>cells</u> following irradiation killed all or many of the viral reservoir cells that are not eliminated by antiretroviral treatment (ART); (2) the CCR5 deletion mutation in the <u>donor cells</u> protected them and their progeny from HIV infection; (3) a "graft versus host" reaction occurred, where the transplanted cells and their progeny recognize the host cells as foreign and attacked and eliminated HIV-positive reservoir cells that survived the irradiation.

Guido Silvestri, from Emory University in Atlanta, USA, and colleagues investigated the relative contribution of the irradiation to eliminate the reservoir of HIV-infected cells. The scientists worked with the animal model of Simian Immunodeficiency Virus (SIV, a close relative of HIV that infects primates and causes a disease similar to AIDS) infection in rhesus macaques. Using a total of six monkeys (three of which served as controls and did not receive transplants) they performed, for the first time, hematopoietic stem cell transplantation in rhesus macaques infected with a chimeric simian/human immunodeficiency virus (SHIV) and treated with ART.

The researchers harvested hematopoetic stem cells from three macaques prior to infection (of all six animals) with SHIV. They also treated the macaques with ART to reduce viral load and mimic the situation in human HIV-infected patients on ART. They then exposed the three monkeys from which they had collected hematopietic stem cells to a high dose of radiation. This killed most of their existing blood and immune cells, including between 94 and 99% of their CD4-T cells—the main target of HIV infection—in the blood. The irradiation was followed by transplantation of each monkey's own virus-free hematopoietic stem cells. The latter can regenerate the blood and immune cells, and did so in all three monkeys within 3 to 6 weeks. Because the transplanted cells are not from a different donor, no graft versus host disease would be expected, and none was observed.



After that time, the scientists stopped ART in all six monkeys. As expected, the virus rebounded rapidly in the control animals. Of the three transplanted animals, two also showed a rapid rebound. The third monkey developed kidney failure two weeks after ART was stopped and was euthanized. It still had undetectable levels of virus in the blood at that time, but post-mortem analysis showed low levels of viral DNA in a number of tissues, arguing that none of the three transplanted monkeys was cured.

The researchers acknowledge a number of limitations of the study, including the small number of monkeys, and the relatively short period of ART prior to irradiation and transplantation. Nonetheless, they say their study "supports the hypothesis that myeloablative total body irradiation can cause a significant decrease in the viral reservoir in blood cells, even though it was not sufficient to eliminate all reservoirs". Their results, they say, suggest that in the cure of the Berlin patient, "the use of the CCR5 mutant donor and/or the presence of graft versus host disease played a significant role".

Having demonstrated in this first test-of-concept study that total body irradiation and <u>hematopoietic stem cell transplantation</u> in ART-treated SIV-infected <u>rhesus macaques</u> is feasible, the researchers express hope that "further studies using this model will provide critical information for the requirements to cure HIV infection in humans".

**More information:** Mavigner M, Watkins B, Lawson B, Lee ST, Chahroudi A, et al. (2014) Persistence of Virus Reservoirs in ART-Treated SHIV-Infected Rhesus Macaques after Autologous Hematopoietic Stem Cell Transplant. *PLoS Pathog* 10(9): e1004406. DOI: 10.1371/journal.ppat.1004406



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