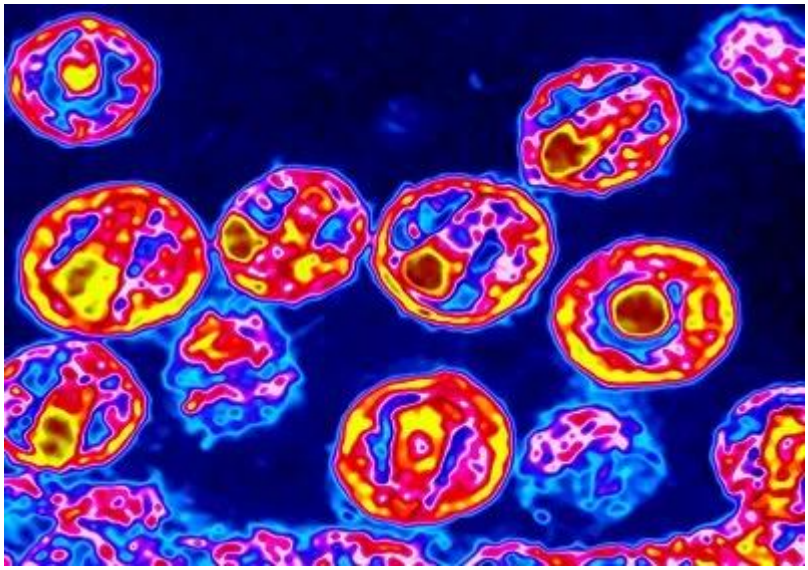
In this case report, a consortium of researchers led by German scientists presented the third case of the human immunodeficiency virus type 1 (HIV-1) cure after allogeneic CCR5Δ32/Δ32 hematopoietic stem cell transplantation (HSCT).

Despite the two cases published to date—the 'London patient' and the 'Berlin patient' describing that allogeneic HSCT may cure HIV-1, the knowledge of immunological and virological correlates of cure is limited.

The HIV-1 persists in the body during antiretroviral therapy in latently infected CD4+ T cells. It has been demonstrated that allogeneic CCR5Δ32/Δ32 HSCT significantly reduces the viral reservoir. However, some immune cell-containing reservoirs are extremely long-lived, partially resistant to chemotherapy regimens used during allogeneic CCR5Δ32/Δ32 HSCT procedures, and may cause viral rebound on analytical treatment interruption.



***About the study***

The authors present a detailed longitudinal virological and extensive immunological analysis of the peripheral blood and tissue compartments of a 53-year-old man who was monitored for more than nine years following allogeneic CCR5Δ32/Δ32 HSCT performed for acute myeloid leukemia (AML).

The patient was diagnosed with HIV-1 clade B positive in January 2008. In October 2010, an antiretroviral treatment regime was introduced, resulting in a continuous suppression of the plasma viral load. In January 2011, the patient was diagnosed with AML M2 according to

the French–American–British classification. He achieved complete hematological remission after chemotherapy. In September 2012, the patient experienced an AML relapse but achieved a second complete remission after chemotherapy.

A systematic search identified a 10/10 HLA-matched unrelated female stem cell donor with a homozygous CCR5Δ32 mutation. 8.74 × 106 unmodified CD34+ peripheral blood stem cells per kg of body weight were transplanted in February 2013. In June 2013, the patient experienced a second AML relapse and achieved a third oncological remission after chemotherapy and four infusions of donor lymphocytes.

In July 2014, the patient experienced a reactivation of cytomegalovirus (duodenal ulcer), herpes simplex virus 2 (genital ulcers and cerebral vasculitis), and Epstein–Barr virus (viremia) but recovered after specific antiviral treatment.

Antiretroviral therapy was continued, and viral HIV-1 DNA and HIV-1 RNA remained undetectable. However, multiple evaluations of the HIV-1 viral reservoir in the peripheral blood and lymphoid and gut tissue before and after analytical treatment interruption revealed sporadic traces of HIV-1 DNA several times. Although rare, residual HIV-1 DNA and HIV-1 RNA were also detected by *in situ* hybridization from histological sections of inguinal lymph node tissue from month 51 and some gut biopsies from month 77.

Importantly, neither HIV-1 p24, HIV-1 RNA nor HIV-1 DNA were detectable in peripheral blood mononuclear cells using a repeated cell culture-based quantitative viral outgrowth assay or intact proviral DNA assay. Negative *in vivo* outgrowth assays in humanized mice confirmed the absence of replication-competent virus in the tested samples.

In the 39th month following HSCT, HIV-1-specific CD8+ T cells were only slightly detected. The frequency of HIV-1-specific T cells was significantly lower than previously seen in other people living with HIV, decreased further below the threshold while still on antiretroviral therapy, and did not increase after analytical treatment interruption.

In the 39th month following HSCT, levels of HIV-1-specific antibodies in peripheral blood were below the cutoff for people living with HIV and comparable to those of HIV-1-negative individuals.

Four years after analytical treatment interruption, the absence of a viral rebound and the absence of immunological correlates of the persistence of HIV-1 antigen were strong evidence of the cure of HIV-1 after CCR5Δ32/Δ32 HSCT. Despite sporadic traces of HIV-1 DNA detected by droplet digital PCR and *in situ* hybridization assays in peripheral T cell

subsets and tissue-derived samples, repeated *ex vivo* quantitative and *in vivo* outgrowth assays in humanized mice did not reveal replication-competent virus. Low levels of immune activation and waning HIV-1-specific humoral and cellular immune responses indicated a lack of ongoing antigen production.

The authors concluded that the absence of a viral rebound and immunological correlates of the HIV-1 antigen persistence four years after analytical treatment interruption provides strong evidence for an HIV-1 cure after CCR5Δ32/Δ32 HSCT.

They noted that their presentation of the third case of HIV-1 cure after allogeneic CCR5Δ32/Δ32 hematopoietic stem cell transplantation provides detailed information about the virological and immunological signature before and after analytical treatment interruption and generates valuable insights that will hopefully guide future cure strategies.

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*Journal Reference*

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