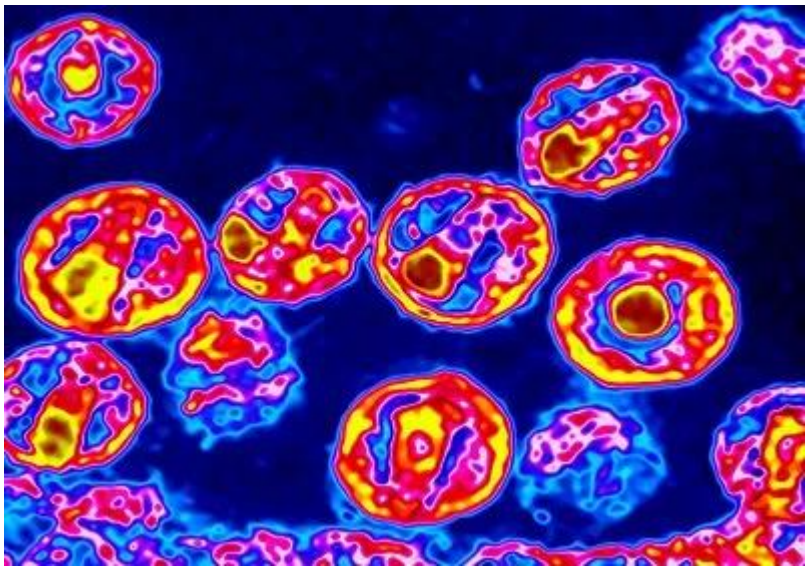
Despite the two cases published to date—the 'London patient' and the 'Berlin patient' describing that allogeneic CCR5Δ32/Δ32 hematopoietic stem cell transplantation (HSCT) may cure the infection with human immunodeficiency virus type 1 (HIV-1), the knowledge of immunological and virological correlates of cure is limited. In this case report, a consortium of researchers led by German scientists presented a detailed and extensive longitudinal virological and immunological analysis of the peripheral blood and tissue compartments in the third case of the HIV-1 cure after allogeneic CCR5Δ32/Δ32 HSCT.

HIV-1 persists in the body during antiretroviral therapy in latently infected CD4+ T-cells. Although allogeneic CCR5Δ32/Δ32 HSCT was shown to reduce the viral reservoir, some reservoirs containing immune cells are extremely long-lived, and partially resistant to chemotherapy regimens used during allogeneic CCR5Δ32/Δ32 HSCT procedures. These cell reservoirs may cause viral rebound on analytical treatment interruption.



***About the Study and Results***

The authors presented a detailed virological and immunological analysis of a 53-year-old patient monitored for more than nine years following allogeneic CCR5Δ32/Δ32 HSCT.

In January 2008, the patient was diagnosed with HIV-1 clade B. 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 acute myeloid leukemia (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 he achieved the second complete remission after chemotherapy.

A systematic search identified a 10/10 HLA-matched unrelated female stem cell donor with a homozygous CCR5Δ32 mutation. In February 2013, 8.74 × 106 unmodified CD34+ peripheral blood stem cells per kg of body weight were transplanted. 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.

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

Importantly, neither HIV-1 p24, RNA nor 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 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. Their frequency further decreased below the threshold during antiretroviral therapy and did not increase after analytical treatment interruption. In addition, in the 39th month following HSCT, HIV-1-specific antibody levels in peripheral blood were below the cutoff for people living with HIV and comparable to HIV-1-negative individuals.

Four years after analytical treatment interruption, the absence of viral rebound and immunological correlates of the HIV-1 antigen persistence were strong evidence of HIV-1 cure 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.

*Conclusion*

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

This 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.

This article was published in Nature Medicine.

*Journal Reference*

Björn-Erik Ole Jensen et al. In-depth virological and immunological characterization of HIV-1 cure after CCR5Δ32/Δ32 allogeneic hematopoietic stem cell transplantation. Nature Medicine (2023) doi.org/10.1038/s41591-023-02213-x (Open Access) https://www.nature.com/articles/s41591-023-02213-x