

# Beyond CCR5Δ32 homozygosity: The second Berlin Patient reveals crucial immune-mediated pathways to HIV cure

Qing Xiao,<sup>1</sup> Huiyu Xiang,<sup>1</sup> Xuejiao Shu,<sup>1</sup> Xiaomei Zhang,<sup>1</sup> Zailin Yang,<sup>1</sup> and Yao Liu<sup>1,\*</sup>

<sup>1</sup>Department of Hematology-Oncology, Hematologic Oncology Intelligent Diagnosis and Treatment Engineering Research Center of Chongqing Education Commission of china, Chongqing University Cancer Hospital, Chongqing 400030, China

\*Correspondence: liuyao77@cqu.edu.cn

Received: December 18, 2025; Accepted: September 4, 2026; Published Online: September 5, 2026; <https://doi.org/10.59717/j.xinn-med.2027.100276>

© 2027 The Author(s). This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).

Citation: Xiao Q., Xiang H., Shu X., et al. (2027). Beyond CCR5Δ32 homozygosity: The second Berlin Patient reveals crucial immune-mediated pathways to HIV cure. *The Innovation Medicine* 5:100276.

By the end of 2024, there were still 40.8 million people living with HIV (PLWH) globally. In 2024 alone, there were 1.3 million new HIV infections worldwide, and approximately 630,000 people died from HIV-related illnesses. Antiretroviral therapy (ART) is highly effective in suppressing HIV replication. However, when ART is discontinued, viral rebound occurs rapidly within four weeks in most PLWH. Therefore, lifelong treatment is required to prevent viral reactivation and disease progression to acquired immunodeficiency syndrome (AIDS). Previously, six individuals with AIDS have been declared "cured" worldwide—namely, the "Berlin patient," the "London patient," the "Düsseldorf patient," the "New York patient," the "City of Hope patient," and the "Geneva patient." The initial proof-of-concept for an HIV cure came from the "Berlin patient," who received a stem cell transplant from a donor homozygous for the CCR5Δ32 mutation. The donor's cells naturally lack the CCR5 receptor, making them resistant to HIV-1 viral entry (R5-tropic). Subsequent rare successful cases, such as the "London patient" and the "Düsseldorf patient," have followed this same approach. This was once widely considered as an essential prerequisite for achieving a cure.<sup>1</sup>

In a recent *Nature* article, Gaebler and colleagues reported the world's seventh case of HIV cure—the "Second Berlin Patient" (Patient B2). This 60-year-old male received an allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an unrelated female donor who carried a CCR5 wild-type/Δ32 heterozygous mutation. ART was discontinued three years after the transplant (in 2018), and for more than seven years since then, no signs of HIV-1 viral replication have been detected. Viral reservoir analysis revealed intact HIV provirus in the patient before the allo-HSCT, but no replication-competent virus was found in the blood or intestinal tissues after transplantation. This study challenges previous understanding: even when the cellular "entry gate" remains partially open, the patient has maintained over seven years of drug-free remission, a hallmark consistent with functional cure of HIV (Figure 1).<sup>2</sup>

The traditional view holds that the CCR5Δ32 homozygous mutation leads to a lack of functional CCR5 receptors on the cell surface, thereby conferring natural resistance of donor-derived immune cells to R5-tropic HIV. However, the earlier "Boston patient" study demonstrated that although patients receiving wild-type CCR5 transplants could maintain viral suppression for a certain period, viral rebound occurred within 3–8 months after treatment discontinuation, seemingly confirming the necessity of CCR5 blockade. The case of Patient B2 challenges this long-held understanding. Notably, Patient B2 is himself a CCR5Δ32 heterozygote. While his CCR5 expression level is lower than that of wild-type individuals, cells remain infectable under specific assays. Among the seven reported cured patients, three were heterozygous recipients (Berlin patient, Düsseldorf patient, and Patient B2), but only Patient B2 received a donor who was heterozygous for CCR5Δ32. This pattern suggests that the CCR5 heterozygous state may confer unique protective effects. From a mechanistic perspective, individuals with CCR5 heterozygosity exhibit approximately 50% lower CCR5 expression compared to wild-type individuals, which may contribute to cure through the following pathways: (1) Reducing viral fitness, thereby limiting the expansion capacity of residual virus; (2) Influencing the evolutionary dynamics of HIV, delaying or preventing viral adaptation to new environments; (3) Favorable disease progression associated with specific CCR5 haplotypes (such as HHC/HHG\*2). Thus, the CCR5 heterozygous state may act as a synergistic factor, working in concert with other mechanisms to facilitate cure.

Unlike other cured cases, the "Geneva patient" achieved remission after receiving a transplant from a wild-type CCR5 donor.<sup>3</sup> This indicates that Patient B2 is not an isolated case but rather compelling evidence of a previously overlooked mechanism—CCR5Δ32 may represent only one piece of the cure puzzle. For heterozygous patients, downregulated CCR5 expression may reduce viral fitness, but this alone cannot explain a complete cure. The true contributor likely resides within the immune system. Researchers have proposed the concept of the "Graft-versus-Reservoir (GVR) effect", where the donor immune system may recognize and eliminate recipient cells harboring integrated HIV proviral DNA. The case of Patient B2 provides strong clinical support for the GVR effect. Despite lacking CCR5-mediated viral resistance, the patient exhibited a significantly reduced HIV reservoir and an extremely low risk of viral rebound. Growing evidence suggests that allogeneic immune responses play a key role in clearing persistent HIV infection.<sup>4,5</sup> The strength of the GVR effect is closely related to immunological differences between the donor and recipient. Patient B2 exhibited an HLA-DPB1 mismatch and multiple minor histocompatibility antigen (miHA) differences predicted to be highly expressed in CD4<sup>+</sup> T cells. These immunological disparities provide a molecular basis for donor T cells to recognize and target recipient-derived HIV-infected cells. The HLA-DPB1 mismatch is particularly noteworthy. Donor-recipient HLA-DPB1 mismatch may induce alloreactivity of donor CD4<sup>+</sup> T cells against recipient antigen-presenting cells and residual CD4<sup>+</sup> T cells. Differences in miHAs may further enhance this targeting, making the GVR effect more precise in eradicating the HIV reservoir. The GVR effect and graft-versus-host disease (GVHD) are essentially different manifestations of the same immune response. A moderate allogeneic immune reaction can help clear the viral reservoir, while an excessive response leads to severe GVHD, which threatens the patient's life. Future research needs to further clarify which specific HLA mismatches and miHA differences contribute most significantly to the GVR effect while maintaining a relatively manageable risk of GVHD.

However, we still cannot overlook that after receiving a transplant from a CCR5 wild-type donor, the "Boston patient" achieved several months of remission upon treatment interruption but ultimately experienced viral rebound. This suggests that the GVHD effect alone may not be sufficient to completely eliminate the reservoir or prevent rebound; the myeloablative conditioning regimen may also play a crucial role. The myeloablative conditioning regimen prior to allo-HSCT, traditionally aims to clear the recipient's bone marrow hematopoietic cells, create space for donor stem cell engraftment, and suppress the recipient's immune system to prevent rejection. In the context of HIV cure, this conditioning regimen assumes an additional critical function: directly killing immune cells harboring the HIV reservoir. The latent HIV reservoir resides predominantly in long-lived memory CD4<sup>+</sup> T cells, which are unresponsive to conventional ART. However, it must be emphasized that conditioning intensity is unlikely to be the sole determining factor. The reduced-intensity regimen used in the Boston cases is typically accompanied by a longer duration of post-transplant immunosuppression and potentially more conservative strategies for GVHD management. The achievement of an HIV cure may be a multi-stage process: (1) Large-scale reservoir reduction during the myeloablative conditioning phase; (2) Ongoing clearance (GVR effect) during early immune reconstitution post-transplantation; (3) Further attrition of residual reservoirs during long-term follow-up. Reservoir analysis in Patient B2 shows a markedly reduced proportion of

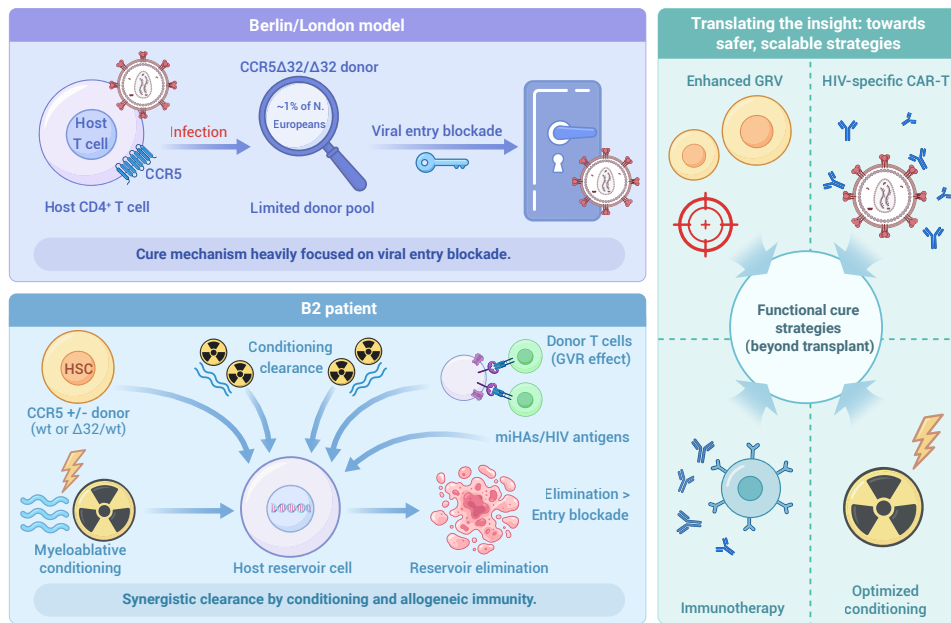


**Figure 1. The lessons learned from the second Berlin (B2) patient and the future research directions in HIV cure** N. Europeans: Northern Europeans; GVR: graft-versus-reservoir; HSC: hematopoietic stem cell; miHA: minor histocompatibility antigen. This figure was created with BioRender.com.

optimizing conditioning regimens to maximize reservoir eradication. Nevertheless, despite the excitement generated by the B2 case, caution remains warranted. First, allo-HSCT carries significant mortality risks and cannot be promoted as a routine HIV treatment. Second, Patient B2's own CCR5 heterozygous status may have been an important synergistic factor in his successful cure—whether this outcome can be generalized to wild-type patients requires further evidence. In the meantime, long-term follow-up remains necessary to confirm a "functional cure" rather than a "delayed rebound", and ultimately provides crucial insights for developing universal strategies that could benefit a broader population of PLWH.

infected cells, supporting this multi-stage clearance model. It demonstrates that the combination of "myeloablation + GVR" can compress the viral reservoir below the threshold of "functional extinction". Notably, different conditioning intensities may differentially impact reservoir clearance. The "Boston patient" received reduced-intensity conditioning, and the eventual viral rebound may be partly attributed to incomplete reservoir eradication. This suggests that it is not merely a question of "clearing and replacing", but rather a delicate balance involving how to achieve the most complete and functional donor immune reconstitution in the shortest possible time and with minimal concomitant immunosuppression.

In summary, the successful cure of Patient B2 provides strong evidence that a homozygous CCR5Δ32 mutation is not a prerequisite for a cure; rather, the synergistic action of the GVR effect and myeloablative conditioning likely constitutes the core mechanism for achieving a cure. This shift in understanding not only expands the potential donor pool but also points the way toward developing safer and more accessible immune-based curative strategies. CCR5Δ32 homozygotes are extremely rare in the general population (approximately 1% in Northern Europeans), whereas heterozygotes account for a much higher proportion—10–20% in European populations. This case implies that the chance of identifying a potentially "curative" donor could increase. Gene therapies could target CCR5 via CRISPR-based editing, ideally coupled with strategies to boost HIV-specific immunity and address viral reservoirs. In practice, this requires integrating CCR5 knockout into conditioning or adoptive T-cell therapies for robust, sustained HIV control. Furthermore, the B2 case suggests that effective reservoir clearance may be more critical than blocking viral entry. Future research directions may include: (1) developing immunomodulatory regimens to enhance the GVR effect; (2) designing CAR-T cell therapies directed against the HIV reservoir; (3) fully leveraging antibody-dependent cellular cytotoxicity (ADCC) to clear reservoirs, combined with immunotherapy using broadly neutralizing antibodies; and (4)

## REFERENCES

- Xiao Q., He S., Wang C., et al. (2025). Deep thought on the HIV cured cases: Where have we been and what lies ahead. *Biomedicine* **15**:378. DOI:10.3390/biom15030378
- Gaebler C., Kor S., Allers K., et al. (2025). Sustained HIV-1 remission after heterozygous CCR5Δ32 stem cell transplantation. *Nature* **650**:701–709. DOI:10.1038/s41586-025-09893-0
- Sáez-Cirión A., Mamez A.C., Avettand-Fenoel V., et al. (2024). Sustained HIV remission after allogeneic hematopoietic stem cell transplantation with wild-type CCR5 donor cells. *Nat. Med.* **30**:3544–3554. DOI:10.1038/s41591-024-03277-z
- Salgado M., Gálvez C., Nijhuis M., et al. (2024). Dynamics of virological and immunological markers of HIV persistence after allogeneic haematopoietic stem-cell transplantation in the IciStem cohort: a prospective observational cohort study. *Lancet HIV* **11**:e389–e405. DOI:10.1016/s2352-3018(24)00090-0
- Wu H.L., Busman-Sahay K., Weber W.C., et al. (2023). Allogeneic immunity clears latent virus following allogeneic stem cell transplantation in SIV-infected ART-suppressed macaques. *Immunity* **56**:1649–1663.e1645. DOI:10.1016/j.immuni.2023.04.019

## FUNDING AND ACKNOWLEDGMENTS

This study was supported by National Natural Science Foundation of China Youth Project (82502702), Prevention and Control of Emerging and Major Infectious Disease-National Science and Technology Major Project (Grant No. 2025ZD01905003), and Chongqing Shapingba District Technology Innovation Project (2025159). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## AUTHOR CONTRIBUTIONS

Qing Xiao wrote the manuscript and made the figure. Huiyu Xiang, Xuejiao Shu, Xiaomei Zhang, Zailin Yang revised the manuscript and figure. Yao Liu had the idea, conducted the supervision and revised the manuscript. All authors contributed to and approved the manuscript.

## DECLARATION OF INTERESTS

The authors declare no competing interests.