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Exploring HIV-1 Cure Strategies: Insights from CCR5Δ32/Δ32 Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract:

Human Immunodeficiency Virus Type 1 (HIV-1) remains a major global health concern despite advances in antiretroviral therapy (ART). ART has transformed HIV-1 into a manageable chronic condition, yet it is not curative, as it does not eliminate viral reservoirs that persist and can reignite infection if treatment is discontinued. A functional cure for HIV-1—control of the virus without ongoing ART—has been a significant focus of research, particularly through approaches such as allogeneic hematopoietic stem cell transplantation (HSCT) with donors harboring the CCR5Δ32 mutation. The CCR5Δ32 mutation prevents HIV-1 from entering host cells by disrupting the CCR5 receptor, a key co-receptor for viral entry, which makes individuals resistant to CCR5-tropic strains of HIV-1. This review mainly focuses a case study of a 53-year-old male with HIV-1 and acute myeloid leukemia (AML), who received a CCR5Δ32/Δ32 HSCT in 2013. The patient exhibited long-term HIV-1 remission, with no viral rebound 48 months after stopping ART. Despite sporadic detection of HIV-1 DNA, no replication-competent virus was found through extensive virological and immunological assessments. The study suggests that the combination of CCR5Δ32/Δ32 transplantation, chemotherapy, and a graft-versus-HIV effect contributed to reducing the viral reservoir and maintaining viral suppression. In addition to other four cases with similar situation from the past, which are London case (2009), Berlin case (2013), Caucasian case (2022), and US case (2022), together supporting the potential of CCR5Δ32/Δ32 HSCT as a functional cure for HIV-1, while highlighting the need for further research to optimize this approach for broader application.

Keywords: HIV-1; CCR5Δ32/Δ32; iStem Cell Transplantation.

1. Introduction

Human Immunodeficiency Virus Type 1 (HIV-1) remains a global health challenge, with an estimated 38 million people living with the virus. Over the past few decades, the introduction of antiretroviral therapy (ART) has dramatically improved the prognosis for those infected, transforming HIV from a fatal disease into a manageable chronic condition. ART works by suppressing HIV replication, reducing viral loads to undetectable levels, and preventing progression to Acquired Immunodeficiency Syndrome (AIDS). Despite its effectiveness, ART does not eliminate the virus from the body, and lifelong adherence is necessary to prevent viral rebound [1,2].

HIV-1 primarily targets CD4+ T cells by binding to the CD4 receptor, which is expressed on the surface of mature T-helper lymphocytes in peripheral blood and lymph nodes, and also on macrophages and dendritic cells, and using coreceptors—primarily CCR5 and CXCR4—to enter and infect these immune cells. Once inside, the virus eventually leads to a slow decline of CD4+ T cells over time and resulting in immune deficiency. This leaves individuals vulnerable to opportunistic infections and malignancies. Two types of HIV—HIV-1 and HIV-2—cause AIDS, with HIV-1 being the more transmissible and virulent form. Although ART suppresses viral replication, it cannot eliminate the HIV-1 reservoirs that harbour the virus [3].

2. Current HIV-1 Treatment & Respective Challenges

2.1 Antiviral Drug Treatment

ART is a common way of HIV treatment, which includes inhibitors targeting viral entry, reverse transcriptase, integrase, and protease enzymes. ART is able to effectively controls viral replication to an undetectable level, but it does not provide a cure. A variety of ART regimens are available, including over 24 FDA-approved drugs categorized into six classes based on their molecular targets. These drugs are distributed into six distinct classes based on their molecular mechanism and resistance profiles [4]. Although ART prevents mother-to-child transmission and serves exposure prophylaxis, A primary obstacle to curing HIV-1 is the persistence of the viral reservoir, a small pool of latently infected cells that harbour replication-competent HIV-1 despite ART. These reservoirs can reignite infection if ART is discontinued [3].

2.2 Vaccines

Containment of the AIDS epidemic will require an effective HIV-1 vaccine. Current vaccine research highlights the need to elicit an HIV-1–specific cytotoxic T lymphocyte (CTL) response for robust immunity. Nonhuman primate models have been critical in assessing the protective immunity conferred by various immunization strategies. While replication-competent AIDS viruses attenuated for pathogenicity by selective gene deletions have shown protective immunity in these models, their long-term safety in human populations remains uncertain [5].

Inactivated virus and subunit vaccines have so far failed to elicit neutralizing antibodies or effective CTL responses against diverse HIV-1 isolates. Consequently, research efforts have shifted toward live vector-based vaccines and plasmid DNA vaccines, which are being tested in both animal models and human trials. As our understanding of the immune response to HIV-1 evolves, new vaccination approaches continue to emerge, holding promise for future prevention strategies [5].

The remarkable heterogeneity of HIV-1, the virus‘s ability to circumvent adaptive immune mechanisms, the failure to elicit broadly neutralizing antibody responses, the prompt formation of dormant viral reservoirs, and the absence of definitive immune correlates of protection pose unparalleled obstacles to the advancement of vaccine strategies [5].

In sum, Strategies to eradicate or control this reservoir have been the focus of intensive research efforts, with stem cell transplantation emerging as one such approach. The concept of a functional cure, in which the virus remains under control without antiretroviral therapy, is gaining increasing attention, especially with evidence from rare cases of HIV-1 remission.

The Role of CCR5 in HIV-1 Entry

CCR5, a chemokine receptor found on the surface of immune cells, plays a pivotal role in the entry of HIV-1 into host cells (Figure 1). The virus binds to the CD4 receptor and uses CCR5 as a coreceptor to gain entry into target cells. However, a naturally occurring mutation, known as CCR5Δ32, results in a truncated, nonfunctional version of the receptor, which prevents HIV-1 from entering cells. Individuals homozygous for this mutation (CCR5Δ32/Δ32) are resistant to CCR5-tropic strains of HIV-1, making this mutation a key target in HIV cure research [6].

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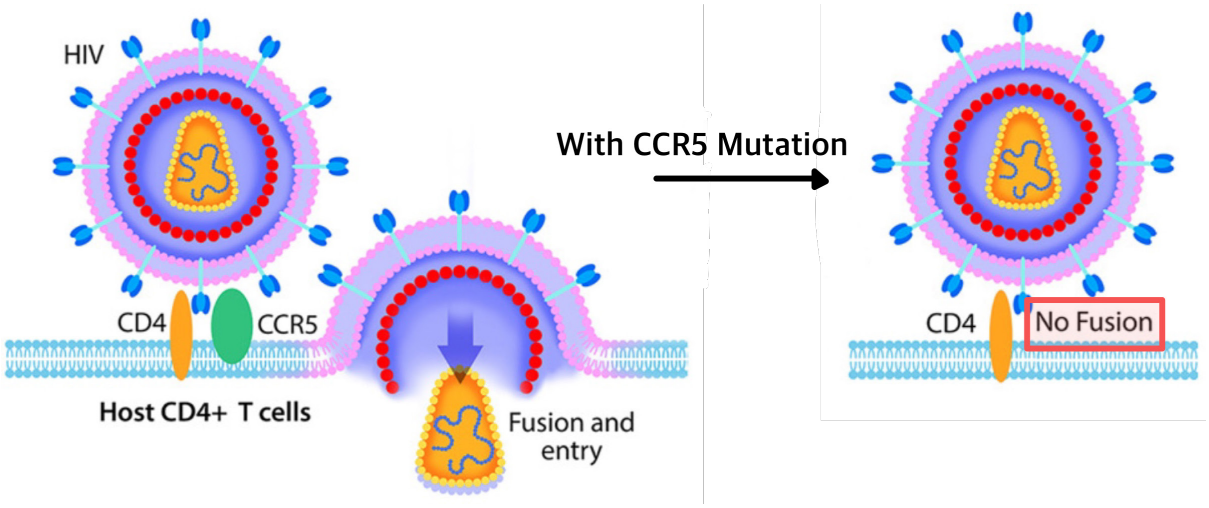

Fig. 1 General mechanism of HIV-1 entry through the binding of CD4 receptor and CCR5 coreceptor (left) and the inhibition of HIV-1 entry in the absence of CCR5 (right) [7].

2.3 Significance of HSCT in HIV-1 Cure

Hematopoietic stem cell transplant (HSCT), commonly designated as bone marrow transplant, entails the infusion of healthy hematopoietic stem cells into patients exhibiting impaired or insufficient bone marrow functionality. This procedure has the potential to produce viable cells that can supplant dysfunctional counterparts in cases like immune deficiency syndromes, hemoglobinopathies, and other diseases [8].

In the context of HIV-1 cure research, HSCT has garnered attention not only for its capacity to reduce the HIV reservoir but also for facilitating what is termed a „graft versus HIV“ effect. This effect involves the introduction of donor-derived immune cells, which may contribute to the eradication of HIV-infected cells within the recipient's draft versus HIV“ effect refers to the immune-mediated clearance of HIV by the donor‘s immune system [9]. After HSCT, the donor‘s immune cells, especially T cells, may recognize and target the remaining HIV-infected cells in the recipient, thereby contributing to the reduction or eradication of the viral reservoir. It has observed that this immune response is promising, but it has not consistently eradicated the virus, possibly due to the infection of donor immune cells by residual HIV [1].

One factor of enhancing this immune response is the use of genetically modified donor cells, such as those carrying the CCR5Δ32 mutation. This mutation provides resistance to HIV by preventing the virus from entering cells, thereby inhibiting the reseeding of the viral reservoir. Moreover, the pre-transplanting regimen, which typically includes chemotherapy, monoclonal antibody therapy, and total body irradiation, further reduces the HIV reservoir by creating an environment that facilitates the engraftment of the donor cells and weakens the patient's immune system [1].

Additional mechanisms, such as the unspecific decay of latently infected cells driven by alloreactivity, may also play a role in reducing the HIV reservoir post-transplant. Alloreactivity, which refers to the ability of recognize and respond to allogeneic (non-self) major histocompatibility complex (MHC) peptides, is often observed in the form of graft-versus-host disease (GvHD) [10]. In this context, donor T cells may attack not only the recipient‘s tissues but also latently infected HIV cells, contributing to the reduction of the viral reservoir. In some cases, the effect of GvHD may be further amplified through donor lymphocyte infusion (DLI), which introduces additional immune cells to target residual HIV-infected cells [1].

Together, these components—the reservoir reduction from g chemotherapy, immune-mediated HIV clearance by donor cells, and the potential contribution of alloreactivity—highlight the multifaceted nature of the HSCT approach in HIV-1 cure research. While these mechanisms have led to successful cases of long-term HIV remission, further research is needed to fully understand and optimize the HSCT process for broader application in HIV-1 treatment [1].

3. Case study

3.1 Patient Profile

The case focuses on a 53-year-old male who was diagnosed with HIV-1 clade B in January 2008, with a CD4+ T cell count of 964 cells/μl and a plasma viral load of 12,850 copies/ml. Following his HIV diagnosis, he began antiretroviral therapy (ART) in October 2010 with HIV-1

plasma viral load: 35,303 copies/ml; 503 CD4+ T cells/μl, which included tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), darunavir, and ritonavir (DRV/r). This regimen effectively suppressed the virus, and the patient remained on ART until the diagnosis of acute myeloid leukaemia (AML) in January 2011 [1].

The patient underwent chemotherapy, achieving complete hematological remission. His treatment included idarubicin, cytarabine, and etoposide, followed by three cycles of high dose cytarabine (HiDAC) consolidation therapy to prevent relapse [1].

To avoid drug-drug interactions, the ART (DRV/r) was switched to raltegravir in March 2011. Despite this, in September 2012, the patient experienced an AML relapse, which was treated successfully, achieving a second complete remission [1].

In February 2013, the patient underwent allogeneic HSCT with a CCR5Δ32/Δ32 mutation to further treat the AML and potentially eliminate HIV-1. 8.74 × 106 unmodified CD34+ peripheral blood stem cells per kg of body weight of stem cells were transplanted from a 10/10 HLA-matched, CCR5Δ32/Δ32 homozygous unrelated female donor. Post-HSCT, the patient received immunosuppressive therapy, which was designed to suppress the immune system for preventing the rejection of transplantation. The initial immunosuppressive therapy consists of a regimen of cyclosporine and mycophenolate mofetil to prevent GvHD, which was later simplified to tacrolimus monotherapy (similar to cyclosporine but often used as an alternative when side effects arise. Despite post-HSCT complications, including a second AML relapse, hepatic GvHD, and reactivation of several viral infections, the patient remained on ART throughout this period with undetectable levels of HIV-1 in his blood [1].

3.2 Results

3.2.1 Long-term Monitoring:

After the CCR5Δ32/Δ32 HSCT in 2013, the patient was closely monitored for over nine years. Despite sporadic detection of HIV-1 DNA at various points, no replication-competent virus was found in the patient‘s peripheral blood, lymphoid or gut tissue before and after analytical treatment interruption (A. Notably, 48 months after stopping ART (November 2018), the patient continued to show no signs of viral rebound, supporting the possibility of a HIV-1 cure [1].

3.2.2 Virological Findings:

Virological assessments revealed sporadic traces of HIV-1 DNA in both peripheral blood and tissue samples post-HSCT. However, all attempts to culture the virus using repeated cell culture-based quantitative viral outgrowth assays and in vivo models (two different humanized mouse models) showed no replication-competent virus. The intact proviral DNA assay, which looks for viable forms of HIV-1 DNA, also produced negative results. These findings strongly indicate that the traces of viral DNA detected were either defective or inactive and incapable of restarting viral replication [1].

Even after ART was stopped 69 months post-HSCT in November 2018, following thorough evaluation. Subsequent testing of four plasma samples collected after the interruption of treatment (ATI) showed no traces of antiretroviral agents. Following ART discontinuation, the patient exhibited no clinical or laboratory indicators of acute retroviral syndrome. Additionally, over a 48-month period of ATI, no rebound of plasma HIV-1 RNA was detected, despite the absence of ART [1].

3.2.3 Immunological Findings:

Immunological profiling demonstrated a gradual decline in the CD4+ T cells and antibody responses following the HSCT. Additionally, the absence of CCR5 expression on the patient’s T cells suggests that any potential reactivation of the virus would be hindered due to the lack of functional receptors necessary for viral entry [1].

Further immunological assessments showed low levels of immune activation, comparable to those of HIV-negative individuals, indicating the absence of active HIV replication. The patient’s CD4+ T cell counts remained stable throughout (Figure 2), compared to previous studies of patients living with HIV after HSCT, and the immune cell composition, particularly in lymphoid and gut tissues, was comparable to healthy controls. No signs of elevated inflammation or gut barrier damage were detected in tissue samples post-HSCT by immunohistochemical staining, further reinforcing the success of the treatment [1].

Extended data from the study demonstrated the stability of CD4+ T cells, reduced naive T cell frequencies, elevated terminally differentiated effector memory T cells (TEMRA), and increased CD56- natural killer (NK) cell frequencies—all findings consistent with previous reports of individuals post-HSCT. These stable immunological markers, combined with the absence of viral rebound, suggest a durable immune response and the absence of active HIV replication post-HSCT [1].

4. Comparison to Other Cases

Four cases of HIV-1 cure via HSCT with the CCR5Δ32 mutation have been documented. These cases, published in 2009 (London patient, male), 2013 (Berlin patient, male), and 2022 (Caucasian patient, male; US patient, fe-

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male), share similarities in patient profiles with previously discussed cases involving HIV-1 and AML.

4.1 2009 (London Patient, 40-year-old Male)

A 40-year-old white male with HIV-1 and newly diagnosed acute myeloid leukaemia (AML, FAB M4 subtype) underwent allogeneic stem cell transplantation using peripheral blood stem cells from an unrelated 9/10 HLA-matched donor homozygous for the CCR5Δ32 allele. Prior to transplantation, the patient had been on highly active antiretroviral therapy (HAART) for four years, with undetectable HIV-1 RNA and a stable CD4 count of 415 cells/μL. After relapsing with AML seven months post-presentation, he received HSCT from a CCR5Δ32 donor. The treatment achieved complete remission of AML, and no detectable HIV-1 RNA was observed post-transplant. Although there were some complications such as severe hepatic toxicity and renal failure, long-term (30 months) follow-up indicated no viral rebound [11].

4.2 2013 (Berlin Patient, Male)

This patient presented an HIV-1 infection treated via allogeneic hematopoietic stem cell transplantation from a homozygous CCR5Δ32 donor. Post-transplant, no HIV DNA or RNA was detected in peripheral blood, lymph nodes, or gut tissues, and no replication-competent virus was observed in the patient's samples. Despite low-level PCR signals, there was no evidence of HIV-1 replication five years after discontinuation of ART, providing strong proof of HIV cure in this case [11]. Results of no detectable HIV DNA/RNA in the patient can also be reflected by the evidence of a sharp decrease of HIV antibody levels throughout the period after transplant, which can be observed in Figure 2.

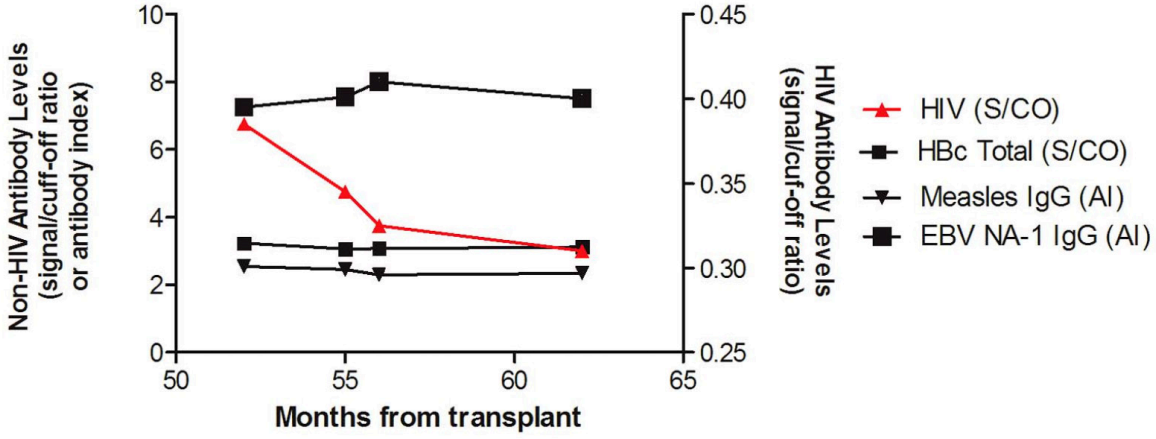

Fig. 2 Changing trends of antibody levels against different pathogens in Berlin patients after transplantation. S/CO = signal/cutoff ratio; AI = antibody index [12].

4.3 2022 (Caucasian Patient, 66-year-old Male)

A 66-year-old Caucasian male diagnosed with HIV-1 in 1988 (CD4 count <100 cells/μL at nadir) was successfully treated for AML with chemotherapy followed by allogeneic HSCT from an unrelated HLA-matched CCR5Δ32 homozygous donor. Following 25 months of ART and a subsequent analytical treatment interruption (ATI), the patient has remained in HIV-1 remission. Testing revealed undetectable HIV-1 RNA levels, with sporadic low-level detection of HIV DNA and RNA in peripheral blood mononuclear cells (PBMCs) and gut tissue [13].

4.4 2022 (US Patient, Female)

This case involves a middle-aged U.S. woman of mixed race diagnosed with both HIV-1 and AML. She underwent a CCR5Δ32/Δ32 cord blood (CB) and CD34-selected haploidentical stem cell transplant (haplo-cord SCT). Fourteen months post-ATI, she remains viraemic (<1 cp/mL). Pre-transplant assessments showed detectable HIV-1 DNA and plasma viremia, but post-transplant, HIV-1 DNA became undetectable in CD4+ T cells and bone marrow (Figure 3). The patient demonstrated no HIV-1 specific T-cell response to Gag and ex-vivo resistance to infection by CCR5/X4 tropic lab strains was confirmed [7].

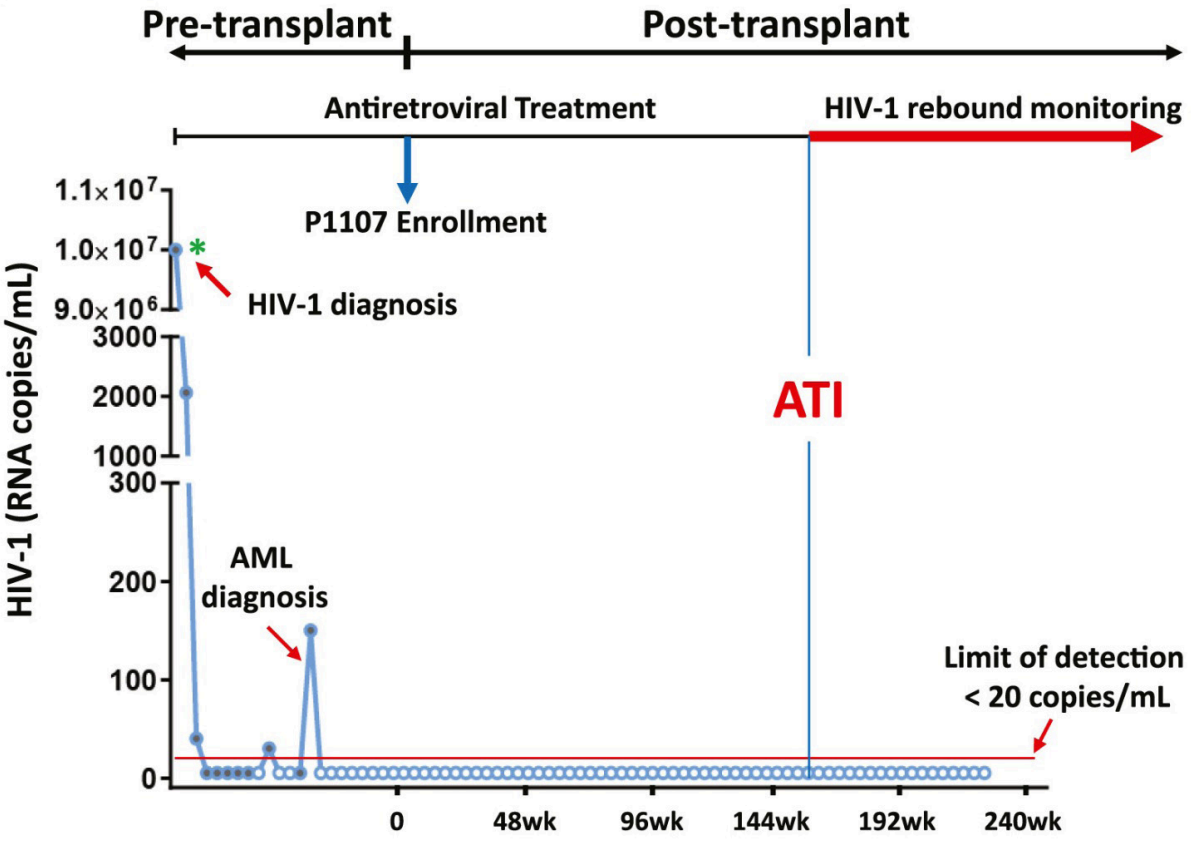

Fig. 3 Changes of HIV-1 viral load during stem cell transplantation and ATI [7].

5. Limitations

5.1 High-Risk Nature of HSCT

While HSCT has demonstrated potential in achieving long-term remission in some individuals with HIV-1, it remains a high-risk procedure. HSCT involves significant risks, including complications from conditioning regimens, GvHD, and infection susceptibility. Furthermore, the complexity and cost of this treatment make it difficult to scale for widespread use in people living with HIV (PLWH). These risks, combined with the lack of standardized protocols, limit HSCT as a broadly applicable HIV-1 cure strategy [1].

5.2 Residual HIV-1 DNA

Despite achieving remission in some cases, traces of HIV-1 DNA have been sporadically detected after HSCT, leading to uncertainties about the potential for viral rebound. It remains unclear whether these residual signals originate from defective viral fragments or an extremely small pool of intact proviruses. This ambiguity arises due to the limited number of cells obtained for analysis and the inaccessibility of anatomical compartments known to harbour HIV-1 reservoirs. As a result, ruling out the presence of replication-competent virus entirely remains challenging [1].

5.3 R5-Tropic vs. X4-Tropic Strain

One crucial factor in the success of CCR5Δ32/Δ32 HSCT is that the patients harboured predominantly R5-tropic virus strains, which rely on the CCR5 receptor for entry into cells [6]. While the modification of the host's immune system through CCR5Δ32/Δ32 transplantation prevents the reseeding of reservoirs for R5-tropic strains, it does not prevent the potential rebound of X4-tropic viruses, which can use the CXCR4 receptor to infect cells. Consequently, the presence of even a small proportion of CXCR4-tropic strains could undermine the long-term success of HSCT [1].

5.4 Need for Larger Studies

The detailed observational data from the few cases of HIV-1 cure after HSCT mentioned previously are insightful but remain anecdotal. The lack of controlled, prospective studies on larger populations of HIV-1 patients limits

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the broader applicability of these findings. Moreover, long-term follow-up is necessary to validate whether the success of these cases can be sustained without viral rebound or other.

6. Future Research Directions

6.1 Gene-Editing Techniques

As an alternative to HSCT, research is exploring the potential of gene-editing technologies, such as CRISPR, to induce the CCR5Δ32 mutation in vivo or ex vivo. This approach could offer a less invasive and potentially safer method for achieving the same protective effect seen in HSCT without the associated risks of transplantation [1].

6.2 Targeting Both CCR5 and CXCR4-Tropic Strains

Current HSCT strategies focus primarily on R5-tropic HIV-1 strains that rely on CCR5 for cell entry. However, HIV-1 can evolve to use the CXCR4 receptor (X4-tropic strains), making it essential to develop therapies that target both CCR5- and CXCR4-tropic viruses. Addressing this broader range of viral tropism will be critical in preventing viral escape and ensuring a durable cure [1].

6.3 Scalable, Low-Risk Cure Strategies

HSCT, while successful in some cases, is not feasible for most people living with HIV due to its complexity and associated risks. Future research should focus on developing scalable and low-risk strategies that can be more widely applicable than HSCT. This could include immune-based therapies, gene therapy, or novel pharmacological interventions aimed at reducing the viral reservoir without the need for invasive procedures [1].

7. Conclusion

The pursuit of a functional cure for HIV-1 has garnered considerable attention over the years, particularly focusing on strategies aimed at targeting and eliminating the viral reservoirs responsible for persistent infection. This review delves into the potential of allogeneic HSCT as a promising cure strategy, especially when using donors with the CCR5Δ32 mutation. CCR5 is an essential co-receptor for HIV-1 entry into CD4+ T cells, and individuals with the CCR5Δ32 homozygous mutation are naturally resistant to HIV-1 infection by CCR5-tropic strains. Thus, transplantation using CCR5Δ32/Δ32 donor cells offers an exciting prospect for rendering patients with HIV-1 infection functionally cured.

A particularly compelling case examined in this review is that of a 53-year-old male who had both HIV-1 and AML. After undergoing HSCT from a CCR5Δ32/Δ32 donor, the patient experienced long-term viral suppression without the need for ART. This case mirrors earlier examples, such as the famous „Berlin Patient," and highlights the potential for HSCT to serve as a means of achieving a sterilizing cure for HIV-1. However, it is critical to note that HSCT is not a broadly applicable treatment, as it comes with significant risks and is typically reserved for individuals requiring transplantation for other life-threatening conditions, such as hematologic malignancies.

While these case studies provide a proof-of-concept for the feasibility of HIV-1 cure through CCR5-targeted strategies, further research is necessary to refine this approach and explore more accessible options. Gene-editing technologies like CRISPR/Cas9, which can mimic the effects of the CCR5Δ32 mutation by directly editing the CCR5 gene in vivo, hold promise for making this strategy more widely applicable and less invasive than HSCT.

In conclusion, although CCR5Δ32/Δ32 HSCT represents a significant breakthrough in the search for an HIV-1 cure, it is not without limitations. Future research should focus on enhancing the safety and scalability of CCR5-based cure strategies to make them available to a broader population of people living with HIV-1. The continued exploration of gene therapy and other curative approaches will be critical to achieving this goal.

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