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The Role of CRISPR-Based Gene Editing in Achieving Functional HIV Cure: A Narrative Review of Preclinical and Clinical Evidence

Nakaziya Obutuzi G.

Faculty of Medicine Kampala International University Uganda

ABSTRACT

Human Immunodeficiency Virus (HIV) remains a global health challenge, with approximately 38 million people living with the virus worldwide. While antiretroviral therapy (ART) has transformed HIV into a manageable chronic condition, it is not a cure, as it fails to eliminate latent viral reservoirs and requires lifelong adherence. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-based gene editing has emerged as a groundbreaking technology with the potential to achieve a functional HIV cure by exercising integrated proviral DNA or editing host genes essential for viral replication, such as CCR5. This narrative review synthesized preclinical and clinical evidence on CRISPR-based interventions for HIV cure, focusing on strategies such as proviral excision, host gene editing, and dual-targeting approaches. Preclinical studies have demonstrated the feasibility of CRISPR in exercising HIV DNA and conferring resistance to infection, while early-phase clinical trials are exploring the safety and efficacy of these interventions in humans. However, significant challenges remain, including off-target effects, delivery efficiency, immune responses, and the persistence of latent reservoirs. The methodology employed in this review involved a comprehensive synthesis of preclinical and clinical studies to evaluate the efficacy, safety, and limitations of CRISPR-based strategies. The findings suggested that CRISPR technology holds immense promise for achieving a functional HIV cure, but interdisciplinary collaboration and careful navigation of ethical and regulatory considerations will be essential for translating these innovations into safe and effective therapies.

Keywords: CRISPR-Cas9, HIV Cure, Gene Editing, Latent Reservoirs, CCR5 Editing.

INTRODUCTION

Human Immunodeficiency Virus (HIV) remains one of the most significant global health challenges, with an estimated 38 million people living with the virus worldwide [1–3]. Antiretroviral therapy (ART) has revolutionized HIV management, transforming it from a fatal disease to a chronic condition. However, ART is not a cure [4, 5]. It requires lifelong adherence, is associated with cumulative toxicities, and fails to eliminate latent viral reservoirs, which can reactivate upon treatment interruption. Consequently, achieving a functional cure defined as sustained viral suppression without the need for ongoing therapy has become a critical goal in HIV research. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-based gene editing has emerged as a groundbreaking technology with the potential to address the limitations of ART [6, 7]. CRISPR-Cas9, a precise and versatile gene-editing tool, enables targeted modifications to the genome, offering the possibility of exercising integrated HIV proviral DNA or editing host genes essential for viral replication, such as CCR5 [8]. The CCR5 co-receptor, which HIV uses to enter CD4+ T cells, has been a focal point since the "Berlin Patient" and "London Patient" were functionally cured of HIV following CCR5Δ32/Δ32 stem cell transplants [9, 10]. CRISPR-Cas9 can theoretically replicate this natural mutation, providing a scalable and less invasive alternative. Preclinical studies have demonstrated the feasibility of CRISPR-based approaches in excising HIV proviral DNA from infected cells and conferring resistance to HIV infection by editing host genes. Early-phase clinical trials are now underway, exploring the safety and efficacy of these interventions in humans. However, significant challenges remain, including off-target effects, delivery efficiency, immune responses to CRISPR components, and the persistence of latent

reservoirs in hard-to-reach anatomical sites. This narrative review synthesizes the current preclinical and clinical evidence on CRISPR-based gene editing for HIV cure research. By evaluating the efficacy, safety, and limitations of these approaches, this review aims to provide a comprehensive understanding of the potential of CRISPR technology to achieve a functional HIV cure and to identify key areas for future research.

CRISPR-Based Strategies for HIV Cure

i. **Excision of Integrated Proviral DNA:** HIV integrates its DNA into the host genome, creating a latent reservoir that is impervious to ART [11]. CRISPR-Cas9 can be programmed to target and excise these proviral sequences, effectively eradicating the virus from infected cells. Preclinical studies have demonstrated the ability of CRISPR to remove HIV DNA from cell lines, primary CD4+ T cells, and animal models. For example, a 2016 study showed that CRISPR could exercise HIV proviral DNA from latently infected T cells, reducing viral replication upon reactivation. However, the efficiency of proviral excision varies, and complete eradication remains challenging due to the heterogeneity of integration sites and the potential for viral escape mutations.

ii. **Editing Host Genes (e.g., CCR5):** Another approach involves editing host genes essential for HIV entry or replication. CCR5, the primary co-receptor for HIV, has been a major target. CRISPR-Cas9 can introduce mutations analogous to the naturally occurring CCR5Δ32 variant, rendering cells resistant to HIV infection. Preclinical studies have shown that CCR5-edited hematopoietic stem cells (HSCs) can engraft and differentiate into HIV-resistant immune cells in humanized mouse models. Clinical trials are now exploring the safety and efficacy of CCR5-edited autologous HSCs in HIV-positive individuals.

iii. **Dual-Targeting Approaches:** Combining proviral excision with host gene editing may enhance the likelihood of achieving a functional cure. For instance, simultaneous targeting of HIV proviral DNA and CCR5 could prevent both viral reactivation and new infections [12]. Preclinical studies have demonstrated the feasibility of this approach, though challenges such as delivery efficiency and off-target effects remain.

Preclinical Evidence

Preclinical studies have provided proof-of-concept for CRISPR-based HIV cure strategies. In vitro studies using cell lines and primary cells have shown that CRISPR can effectively excise HIV proviral DNA or edit host genes like CCR5 [13, 14]. Animal models, particularly humanized mice, have further validated these findings, demonstrating reduced viral loads and reservoir sizes following CRISPR intervention. However, these studies also highlight limitations, such as incomplete excision of proviral DNA, off-target effects, and immune responses to CRISPR components.

Clinical Evidence

Early-phase clinical trials are now evaluating CRISPR-based interventions in humans. For example, a recent Phase I trial tested the safety of CCR5-edited autologous HSCs in HIV-positive individuals [15]. Preliminary results indicated successful engraftment and persistence of edited cells, with no serious adverse events. Another trial is exploring the use of CRISPR to excise proviral DNA in ART-suppressed individuals. While these studies are promising, they are still in their infancy, and long-term efficacy and safety data are lacking.

Challenges and Limitations

i. **Off-Target Effects:** CRISPR-Cas9 can induce unintended mutations at off-target sites, raising concerns about genomic instability and oncogenic potential [16]. Advances in high-fidelity Cas variants and improved delivery systems are addressing this issue, but it remains a significant barrier to clinical translation.

ii. **Delivery Efficiency:** Efficient delivery of CRISPR components to target cells, particularly latent reservoirs in hard-to-reach anatomical sites, is a major challenge. Viral vectors, lipid nanoparticles, and ex vivo editing strategies are being explored to improve delivery.

iii. **Immune Responses:** The immune system may recognize CRISPR components as foreign, leading to immune activation or rejection of edited cells. Strategies to mitigate immune responses, such as using immune-evasive Cas proteins, are under investigation.

iv. **Persistence of Latent Reservoirs:** Despite CRISPR intervention, residual latent reservoirs may persist, necessitating combination approaches with latency-reversing agents or immune-based therapies.

Future Directions

i. **Enhancing Precision and Efficiency:** Developing high-fidelity Cas variants and optimizing delivery systems will be critical for improving the precision and efficiency of CRISPR-based interventions.

ii. **Combination Therapies:** Combining CRISPR with other cure strategies, such as latency-reversing agents, broadly neutralizing antibodies, or therapeutic vaccines, may enhance efficacy [17].

iii. **Long-Term Safety Studies:** Longitudinal studies are needed to assess the long-term safety and durability of CRISPR-based interventions in humans.

iv. **Ethical and Regulatory Considerations:** The ethical implications of germline editing and the regulatory landscape for CRISPR-based therapies must be carefully navigated.

CONCLUSION

CRISPR-based gene editing represents a transformative approach in the quest for a functional HIV cure. Preclinical and early clinical studies have demonstrated the feasibility of excising proviral DNA and editing host genes like CCR5, offering hope for a future where HIV can be effectively cured. However, significant challenges remain, including off-target effects, delivery efficiency, immune responses, and the persistence of latent reservoirs. Addressing these challenges through technological advancements, combination therapies, and rigorous clinical testing will be essential for realizing the potential of CRISPR in HIV cure research. The progress made thus far underscores the promise of CRISPR technology, but it also highlights the complexity of translating these innovations into safe and effective therapies. As research continues to advance, interdisciplinary collaboration among scientists, clinicians, ethicists, and policymakers will be crucial to navigating the scientific, ethical, and regulatory landscapes. While the road ahead is complex, the potential to achieve a functional HIV cure through CRISPR-based gene editing offers hope for millions of individuals living with HIV worldwide, marking a significant step forward in the fight against this global health challenge.

REFERENCES

1. Ugo Alum, E., Okechukwu, U.P., Ifeanyi Obeagu, E., Maduabuchi Aja, P.: Reducing HIV Infection Rate in Women: A Catalyst to reducing HIV Infection pervasiveness in Africa. (2023). https://doi.org/10.58538/IJIAR/2048
2. Obeagu, E.I., Obeagu, G.U., Alum, E.U., Ugwu, O.P.-C.: Understanding the Impact of HIV-Associated Bone Marrow Alterations on Erythropoiesis. INOSR Scientific Research. 10, 1–11 (2023). https://doi.org/10.59298/INOSRSR/2023/1.2.12222
3. Painter, M.: Mechanisms of Human Immunodeficiency Virus (HIV) Persistence and Strategies to Elicit Cytotoxic T Lymphocyte-Mediated Clearance of HIV-Infected Cells. (2020). https://doi.org/10.7302/31
4. Balasubramaniam, M., Pandhare, J., Dash, C.: Immune Control of HIV. J Life Sci (Westlake Village). 1, 4 (2019). https://doi.org/10.36069/jols/20190603
5. Obeagu, E.I., Obeagu, G.U., Alum, E.U., Ugwu, O.P.-C.: Comprehensive Review of Antiretroviral Therapy Effects on Red Blood Cells in HIV Patients. INOSR Experimental Sciences. 12, 63–72 (2023). https://doi.org/10.59298/INOSRES/2023/6.3.21322
6. Alum, E. U., Obeagu, E. I., Ugwu, O. P. C., Samson, A. O., Adepoju, A. O., Amusa, M. O. Inclusion of nutritional counseling and mental health services in HIV/AIDS management: A paradigm shift. Medicine (Baltimore). 2023;102(41):e35673. http://dx.doi.org/10.1097/MD.0000000000035673.
7. Modell, A.E., Lim, D., Nguyen, T.M., Sreekanth, V., Choudhary, A.: CRISPR-based therapeutics: current challenges and future applications. Trends Pharmacol Sci. 43, 151–161 (2022). https://doi.org/10.1016/J.TIPS.2021.10.012/ASSET/62136F36-26C0-4DB0-AB67-B5D6C338D981/MAIN.ASSETS/GR2.SML
8. Alum, E.U., Uti, D.E., Ugwu, O.P.C., Alum, B.N.: Toward a cure - Advancing HIV/AIDs treatment modalities beyond antiretroviral

therapy: A Review. Medicine (United States). 103, e38768 (2024). https://doi.org/10.1097/MD.0000000000038768

9. Kalidasan, V., Theva Das, K.: Lessons Learned from Failures and Success Stories of HIV Breakthroughs: Are We Getting Closer to an HIV Cure? Front Microbiol. 11, 517665 (2020). https://doi.org/10.3389/FMICB.2020.00046/PDF
10. Chen, X., Jia, L., Zhang, X., Zhang, T., Zhang, Y.: One arrow for two targets: potential co-treatment regimens for lymphoma and HIV. Blood Rev. 55, 100965 (2022). https://doi.org/10.1016/J.BLRE.2022.100965
11. Li, K., Zhang, Q.: Eliminating the HIV tissue reservoir: current strategies and challenges. Infect Dis. 56, 165–182 (2024). https://doi.org/10.1080/23744235.2023.2298450
12. Karuppusamy, K. V., Babu, P., Thangavel, S.: The Strategies and Challenges of CCR5 Gene Editing in Hematopoietic Stem and Progenitor Cells for the Treatment of HIV. Stem Cell Rev Rep. 17, 1607–1618 (2021). https://doi.org/10.1007/S12015-021-10145-7/METRICS
13. Chen, S., Yu, X., Guo, D.: CRISPR-Cas Targeting of Host Genes as an Antiviral Strategy. Viruses 2018, Vol. 10, Page 40. 10, 40 (2018). https://doi.org/10.3390/V10010040
14. Xxx, C., Bella, R.: Gene Editing Technologies Based on CRISPR-CAS9 System for The Treatment of HIV: Studies In Vitro And In Vivo. (2018). https://doi.org/10.13130/R-BELLA_PHD2018-01-25
15. Karuppusamy, K. V., Demosthenes, J.P., Venkatesan, V., Christopher, A.C., Babu, P., Azhagiri, M.K., Jacob, A., Ramalingam, V.V., Rangaraj, S., Murugesan, M.K., Marepally, S.K., Varghese, G.M., Srivastava, A., Kannangai, R., Thangavel, S.: The CCR5 Gene Edited CD34+CD90+ Hematopoietic Stem Cell Population Serves as an Optimal Graft Source for HIV Gene Therapy. Front Immunol. 13, 792684 (2022). https://doi.org/10.3389/FIMMU.2022.792684/BIBTEX
16. Han, H.A., Pang, J.K.S., Soh, B.S.: Mitigating off-target effects in CRISPR/Cas9-mediated in vivo gene editing. J Mol Med. 98, 615–632 (2020). https://doi.org/10.1007/S00109-020-01893-Z/TABLES/2
17. Schwarzer, R., Gramatica, A., Greene, W.C.: Reduce and Control: A Combinatorial Strategy for Achieving Sustained HIV Remissions in the Absence of Antiretroviral Therapy. Viruses 2020, Vol. 12, Page 188. 12, 188(2020).https://doi.org/10.3390/V12020188

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