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

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## ABSTRACT

The persistence of latent viral reservoirs remains a significant barrier to achieving a functional cure for HIV, despite the success of antiretroviral therapy (ART) in suppressing viral replication. CRISPR-based gene editing has emerged as a transformative tool with the potential to target and exercise integrated proviral DNA, offering a novel approach to eradicating HIV reservoirs. This narrative review synthesized preclinical and clinical evidence on the role of CRISPR in achieving a functional HIV cure, focusing on its mechanisms, applications, and therapeutic potential. Preclinical studies in cell lines, primary cells, and animal models have demonstrated the ability of CRISPR to disrupt HIV DNA and reduce viral load, while early-phase clinical trials have explored its safety and feasibility in humans. However, challenges such as off-target effects, immune responses, and the heterogeneity of latent reservoirs persist. This review highlighted the need for optimized delivery systems, combinatorial therapeutic strategies, and long-term safety assessments to advance CRISPR-based therapies. By integrating CRISPR with other modalities, such as latency-reversing agents and immune-based therapies, there is potential to achieve sustained viral suppression and bring us closer to a functional HIV cure. This article employed a narrative review methodology, drawing on a comprehensive analysis of preclinical and clinical studies to evaluate the current state and future directions of CRISPR-based gene editing in HIV cure research.

**Keywords:** CRISPR-Cas9, HIV Cure, Latent Reservoirs, Gene Editing, Antiretroviral Therapy (ART).

## INTRODUCTION

The human immunodeficiency virus (HIV) remains one of the most formidable global health challenges, with approximately 38 million people living with the virus worldwide [1–3]. Despite remarkable advancements in antiretroviral therapy (ART), which has transformed HIV from a fatal disease to a manageable chronic condition, a definitive cure remains elusive. ART effectively suppresses viral replication, reduces morbidity and mortality, and prevents transmission [4, 5]. However, it does not eradicate the virus due to the persistence of latent viral reservoirs, which are immune to both the immune system and current pharmacological interventions. These reservoirs, primarily composed of integrated proviral DNA within the host genome, can reactivate upon ART cessation, leading to viral rebound. Thus, achieving a functional cure defined as sustained viral suppression without the need for ongoing ART has become a paramount goal in HIV research. In recent years, CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)-based gene editing has emerged as a revolutionary tool in molecular biology, offering unprecedented precision in targeting and modifying specific DNA sequences [6, 7]. This technology, derived from bacterial adaptive immune systems, utilizes a guide RNA (gRNA) to direct the Cas9 endonuclease to a target site, enabling precise gene disruption, correction, or insertion. The potential of CRISPR to exercise integrated HIV proviral DNA from the host genome has sparked considerable interest in its application for HIV cure strategies. Preclinical studies have demonstrated the feasibility of CRISPR in targeting and inactivating HIV DNA in cell lines, primary cells, and animal models. Early-phase clinical trials have further explored its safety and efficacy, albeit with mixed results. This narrative review aims to synthesize the current preclinical and clinical evidence on the role of CRISPR-based gene editing in achieving a functional HIV cure, highlighting its potential, limitations, and future directions.

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## CRISPR-Based Gene Editing: Mechanisms and Applications in HIV Research

CRISPR-Cas9 technology operates through a relatively simple yet highly efficient mechanism. The system consists of two key components: the Cas9 endonuclease and a single guide RNA (sgRNA). The sgRNA is designed to be complementary to a specific DNA sequence, guiding Cas9 to the target site where it induces a double-strand break (DSB) [8]. In the context of HIV, the primary goal is to target and disrupt the integrated proviral DNA within the host genome, thereby preventing viral replication and reactivation. Several strategies have been explored, including the direct excision of proviral DNA, disruption of essential viral genes, and modulation of host factors critical for viral entry and replication. Preclinical studies have demonstrated the potential of CRISPR to target conserved regions of the HIV genome, such as the long terminal repeats (LTRs) and structural genes like *gag* and *pol* [9]. By disrupting these regions, researchers have successfully achieved viral suppression in cell cultures and animal models. Additionally, CRISPR has been employed to target host factors such as the CCR5 co-receptor, which is essential for HIV entry into CD4+ T cells. The disruption of CCR5 mimics the natural resistance observed in individuals with the CCR5-Δ32 mutation, who are highly resistant to HIV infection. These findings underscore the versatility of CRISPR in addressing both viral and host targets, offering a multifaceted approach to HIV cure strategies.

## Preclinical Evidence: From Cell Lines to Animal Models

The preclinical development of CRISPR-based HIV therapies has progressed through several stages, beginning with in vitro studies in cell lines and primary cells, followed by validation in animal models. Early experiments demonstrated that CRISPR could effectively excise integrated HIV proviral DNA from infected cell lines, leading to a significant reduction in viral replication [10]. These studies provided proof-of-concept evidence that CRISPR could target and disrupt the HIV genome with high specificity and efficiency. Subsequent research extended these findings to primary human cells, including CD4+ T cells and macrophages, which are critical reservoirs of latent HIV. CRISPR-mediated disruption of proviral DNA in these cells resulted in sustained viral suppression, even after the cessation of ART [11]. Importantly, these studies also highlighted the challenges of achieving complete eradication, as residual proviral DNA persisted in some cells, potentially due to inefficient delivery or off-target effects. Animal models, particularly humanized mice, have played a pivotal role in evaluating the in vivo efficacy of CRISPR-based therapies [12, 13]. These models, which are engrafted with human immune cells, closely mimic HIV infection in humans. Studies in humanized mice have shown that CRISPR can reduce viral load and delay viral rebound following ART interruption. However, the extent of viral suppression varied, with some studies reporting near-complete eradication and others observing partial effects. These discrepancies may be attributed to differences in CRISPR delivery methods, target selection, and the inherent limitations of animal models in recapitulating human HIV infection.

## Clinical Evidence: Early-Phase Trials and Safety Considerations

The translation of CRISPR-based therapies from preclinical models to clinical trials has been met with both enthusiasm and caution. Early-phase clinical trials have primarily focused on assessing the safety and feasibility of CRISPR in humans, with a secondary emphasis on efficacy. One of the pioneering studies involved the ex vivo modification of hematopoietic stem cells (HSCs) using CRISPR to disrupt the CCR5 gene [14, 15]. The modified HSCs were then infused into HIV-positive patients, with the aim of reconstituting the immune system with CCR5-deficient cells resistant to HIV infection. Preliminary results indicated that the procedure was well-tolerated, with no serious adverse events reported. However, the efficacy of this approach in achieving sustained viral suppression remains to be fully determined. Another clinical trial explored the use of CRISPR to directly target and excise integrated HIV proviral DNA infected individuals. This study employed a novel delivery system to deliver CRISPR components to latent reservoirs in vivo. While the treatment was shown to be safe, the reduction in viral load was modest, and viral rebound occurred after ART cessation. These findings underscore the challenges of achieving complete eradication of latent reservoirs, which are highly heterogeneous and may require combinatorial approaches. Safety remains a paramount concern in the clinical application of CRISPR. Off-target effects, wherein CRISPR induces unintended modifications in the host genome, pose a significant risk. These off-target mutations could potentially lead to oncogenesis or other adverse outcomes. Advances in CRISPR technology, such as the development of high-fidelity Cas9 variants and improved gRNA design algorithms, have mitigated but not eliminated this risk. Additionally, immune responses to CRISPR components, particularly Cas9, could limit the efficacy and safety of these therapies. Ongoing research is focused on optimizing delivery methods, enhancing specificity, and minimizing immunogenicity to improve the therapeutic potential of CRISPR in HIV cure strategies.

## Challenges and Future Directions

Despite the promising preclinical and early clinical results, several challenges must be addressed to realize the full potential of CRISPR-based gene editing in achieving a functional HIV cure. One of the primary obstacles is the delivery of CRISPR components to latent reservoirs, which are widely distributed throughout the body and often reside in immunologically privileged sites [16]. Current delivery methods, including viral vectors and nanoparticles,

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have limitations in terms of efficiency, specificity, and scalability. Developing targeted delivery systems that can reach these reservoirs without eliciting significant immune responses is a critical area of ongoing research. Another challenge is the heterogeneity of latent reservoirs, which harbor diverse proviral sequences with varying degrees of integrity and activity. This heterogeneity complicates the design of gRNAs that can universally target all proviral variants [17]. Combinatorial approaches, involving multiple gRNAs or the integration of CRISPR with other gene-editing technologies, may be necessary to achieve comprehensive viral eradication. Furthermore, the long-term safety and durability of CRISPR-based therapies remain to be fully elucidated. While early-phase trials have demonstrated short-term safety, the potential for off-target effects and immune responses necessitates long-term monitoring. Advances in genome-wide off-target detection methods and the development of strategies to mitigate immune responses will be crucial in addressing these concerns. Future research should also explore the integration of CRISPR with other therapeutic modalities, such as latency-reversing agents, immune-based therapies, and broadly neutralizing antibodies. These combinatorial approaches could synergistically enhance the efficacy of CRISPR by reactivating latent viruses, boosting immune responses, and targeting residual viral reservoirs. Additionally, the development of personalized CRISPR therapies, tailored to the unique viral and host factors of individual patients, may improve outcomes and minimize adverse effects.



## CONCLUSION

CRISPR-based gene editing represents a groundbreaking advancement in the quest for a functional HIV cure. Preclinical studies have demonstrated its potential to target and disrupt integrated proviral DNA, offering a promising avenue for eradicating latent reservoirs. Early-phase clinical trials have provided valuable insights into the safety and feasibility of CRISPR in humans, albeit with modest efficacy thus far. However, significant challenges remain, including the delivery of CRISPR components to latent reservoirs, the heterogeneity of proviral sequences, and the risk of off-target effects and immune responses.

Addressing these challenges will require continued innovation in CRISPR technology, delivery systems, and combinatorial therapeutic approaches. The integration of CRISPR with other modalities, such as latency-reversing agents and immune-based therapies, holds promise in achieving sustained viral suppression. As research progresses, the potential for CRISPR to transform the landscape of HIV treatment and bring us closer to a functional cure becomes increasingly tangible. While the road ahead is complex, the convergence of scientific ingenuity and collaborative effort offers hope for a future free from the burden of HIV.

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