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The Impact of CRISPR-Cas9 Gene Editing Versus Antiretroviral Therapy Alone on HIV Reservoir Reduction in Infected Humanized Mice

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ABSTRACT

The persistent latent HIV reservoir remains the primary obstacle to achieving a cure for HIV infection, despite the significant success of highly active antiretroviral therapy (ART). While ART effectively suppresses active viral replication, it does not eliminate the integrated provirus, necessitating lifelong treatment with its associated burdens. This review critically examined the impact of CRISPR-Cas9 gene editing on HIV reservoir reduction in infected humanized mice, directly comparing its efficacy to antiretroviral therapy alone. To compile this review, a comprehensive analysis of peer-reviewed scientific literature focusing on preclinical studies utilizing established humanized mouse models for HIV infection and latency was conducted, synthesizing data on reservoir quantification and intervention outcomes. The review elucidated the precise mechanisms by which CRISPR-Cas9 targets integrated proviral DNA, either through functional inactivation or complete genomic excision, offering a fundamentally different approach from ART's mechanism of merely inhibiting new viral replication. Experimental findings consistently demonstrate that CRISPR-Cas9 leads to a significant and measurable reduction in total HIV DNA and, critically, intact proviral DNA within various tissues of humanized mice. This reduction is a substantial improvement over the minimal impact observed with ART alone during comparable study durations. Despite challenges concerning in vivo delivery efficiency, potential off-target effects, and host immune responses to gene editing components, the compelling preclinical evidence strongly supports advancing CRISPR-Cas9 as a transformative and potentially curative strategy for eliminating the latent HIV reservoir.

Keywords: CRISPR-Cas9**,** HIV Reservoir**,** Gene Editing**,** Antiretroviral Therapy (ART)**,** Humanized Mice.

INTRODUCTION

The global health landscape has been profoundly impacted by the Human Immunodeficiency Virus (HIV) epidemic, which continues to pose a significant public health challenge despite remarkable advancements in treatment [1, 2]. The advent of highly active antiretroviral therapy (HAART) has transformed HIV infection from a rapidly fatal disease into a manageable chronic condition, dramatically improving the lifespan and quality of life for millions living with HIV [3]. HAART achieves this by effectively suppressing viral replication to undetectable levels in the peripheral blood, thereby preventing disease progression and onward transmission. However, HAART does not eradicate the virus from the body. Instead, HIV establishes latent reservoirs, primarily within resting memory CD4+ T cells and other cell types, where the viral genome is integrated into the host cell's DNA and remains transcriptionally silent. These latent reservoirs are the primary barrier to an HIV cure, as they persist despite long-term ART and can rapidly reactivate upon treatment interruption, leading to viral rebound. The persistence of these reservoirs necessitates lifelong ART, which is associated with considerable challenges, including drug-related toxicities, adherence issues, significant financial burdens, and the potential for drug resistance development. Consequently, the pursuit of strategies to reduce or eliminate the latent HIV reservoir remains a central focus of HIV cure research.

Traditional "shock and kill" strategies aim to reactivate the latent virus (shock) and then clear the reactivated cells through enhanced immune responses or intensified ART (kill) [4]. While promising, these approaches have met with limited success in significantly reducing the reservoir size in clinical trials, primarily due to the inefficiency of

latency reversal agents and the immune system's inability to effectively clear all reactivated cells. This has spurred exploration into more direct and potentially curative interventions, among which gene editing technologies stand out as revolutionary. Gene editing offers the unprecedented ability to precisely modify the host or viral genome, presenting a novel approach to tackle the integrated provirus directly.

The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 system, originally a bacterial adaptive immune system, has rapidly emerged as the leading gene editing tool due to its simplicity, efficiency, and remarkable precision [5]. CRISPR-Cas9 can be programmed with a guide RNA (gRNA) to target specific DNA sequences, where the Cas9 nuclease then creates a double-strand break (DSB) [6]. In the context of HIV, CRISPR-Cas9 holds immense potential to either disrupt essential viral genes within the integrated provirus, thereby inactivating it, or to excise the proviral DNA completely from the host genome. This direct targeting of the integrated reservoir distinguishes gene editing from conventional ART, which only inhibits new rounds of infection and active replication. This review will systematically explore the impact of CRISPR-Cas9 gene editing on HIV reservoir reduction in infected humanized mice, comparing its efficacy against antiretroviral therapy alone. It will delve into the methodological considerations of using humanized mouse models, detail the mechanisms of CRISPR-Cas9 in this context, analyze current experimental findings, and discuss the implications for future HIV cure strategies.

Methodological Considerations in Humanized Mouse Models for HIV Research

Humanized mouse models have become indispensable tools in HIV cure research, bridging the gap between *in vitro* studies and human clinical trials [7]. These models are engineered to possess a human immune system, thereby allowing for robust HIV infection, latency establishment, and assessment of therapeutic interventions in an *in vivo* setting that closely mimics human pathophysiology. The most used humanized mouse models for HIV research involve immunodeficient mice, typically NOD. Cg-Prkdcscid Il2rgtm1Wjl/SzJ (NSG) or similar strains, which lack mature T, B, and NK cells [8]. These mice are then engrafted with human hematopoietic stem cells (HSCs), fetal liver, or thymus/liver tissues, leading to the reconstitution of a functional human immune system, including human CD4+ T cells, macrophages, and dendritic cells. This engraftment allows for systemic HIV infection, development of viremia, CD4+ T cell depletion, and, crucially, the establishment of persistent viral reservoirs that are responsive to ART.

The utility of humanized mice in evaluating HIV cure strategies, particularly gene editing, lies in several key aspects. Firstly, they permit the study of HIV latency and persistence *in vivo* in a way that *in vitro* models cannot fully replicate, including the complex interplay between different cell types and anatomical compartments. Secondly, they allow for the assessment of various routes of delivery for gene editing components (e.g., viral vectors like AAV or lentiviral vectors, or lipid nanoparticles), as well as the biodistribution and potential off-target effects of the gene editing machinery. Thirdly, and most importantly for this review, humanized mice enable the quantitative measurement of HIV reservoir size before and after interventions using techniques such as quantitative viral outgrowth assays (qVOA), total HIV DNA measurements, and intact proviral DNA assays (IPDA). These assays provide critical readouts for evaluating the efficacy of reservoir reduction strategies.

However, it is also important to acknowledge the limitations of humanized mouse models. While they recapitulate many aspects of human HIV infection, they are not perfect replicas. The immune system reconstitution is often incomplete, lacking the full diversity and maturity of human lymphoid organs. Differences in human and mouse physiology, such as metabolic rates and drug pharmacokinetics, can also influence experimental outcomes. Furthermore, the kinetics of HIV infection and latency establishment in mice may differ from humans, potentially affecting the generalizability of findings, especially regarding the long-term persistence of the reservoir. Despite these limitations, humanized mice remain the gold standard for preclinical evaluation of HIV cure interventions, providing invaluable insights into the *in vivo* efficacy and safety of novel approaches like CRISPR-Cas9.

Mechanisms of CRISPR-Cas9 in Targeting the HIV Provirus

CRISPR-Cas9 offers several distinct strategies for targeting the integrated HIV provirus within host cell genomes [9]. The primary approach involves designing guide RNAs (gRNAs) to direct the Cas9 nuclease to specific, highly conserved regions within the HIV long terminal repeats (LTRs) or essential coding sequences (e.g., *gag*, *pol*, *env*) [10].

One major strategy is proviral inactivation. By introducing double-strand breaks (DSBs) within critical viral genes, CRISPR-Cas9 can disrupt the gene's coding sequence. When these DSBs are repaired by the cell's non-homologous end joining (NHEJ) pathway, it often leads to insertions or deletions (indels) at the repair site. If these indels occur within an essential viral gene, they can introduce frameshifts or premature stop codons, effectively rendering the provirus replication-incompetent. This permanently "silences" or "disarms" the integrated virus, preventing it from producing functional viral proteins upon reactivation.

A more ambitious and potentially curative strategy is proviral excision. By designing two gRNAs to flank a significant portion of the integrated provirus (e.g., one targeting the 5' LTR and another targeting the 3' LTR), Cas9 can induce two simultaneous DSBs [11]. If the cell's repair machinery, then joins these two distal ends, the entire intervening proviral DNA sequence can be excised, effectively removing the virus from the host cell genome. This "cut-and-paste" mechanism represents a true removal of the integrated reservoir, potentially leading to a sterilizing cure if achieved in a sufficient proportion of infected cells. This approach holds the promise of not only preventing viral rebound but also eliminating the source of ongoing low-level inflammation and immune activation associated with persistent proviral DNA.

The choice of target regions within the HIV genome is critical. Conserved regions are preferred to ensure broad applicability across diverse HIV strains and to minimize the risk of viral escape through mutation. The LTRs are particularly attractive targets as they are crucial for viral gene expression and integration, and they are present at both ends of the integrated provirus, facilitating excision. Furthermore, the specificity of gRNAs is paramount to avoid off-target editing in the host cell genome, which could lead to genotoxicity or unintended cellular dysfunction [12]. Delivery methods for the CRISPR-Cas9 components (Cas9 enzyme or mRNA encoding Cas9, and gRNAs) are also crucial, with viral vectors (e.g., Adeno-associated virus (AAV) for *in vivo* delivery) and lipid nanoparticles being actively investigated for their efficiency and safety in reaching relevant cell populations, including latently infected cells [13].

Impact of CRISPR-Cas9 Gene Editing on HIV Reservoir Reduction: Experimental Findings

Numerous studies utilizing humanized mouse models have provided compelling evidence for the efficacy of CRISPR-Cas9 in reducing HIV reservoirs. These experiments typically involve infecting humanized mice with HIV to establish a stable infection and latent reservoir, often followed by a period of ART to mimic the clinical setting of viral suppression. Subsequently, the CRISPR-Cas9 components are delivered, and the impact on the viral reservoir is assessed.

Early studies demonstrated that systemic delivery of CRISPR-Cas9 via viral vectors (e.g., AAV9) encoding Cas9 and gRNAs targeting conserved regions of the HIV LTR or gag gene could significantly reduce HIV viral load in the peripheral blood of infected humanized mice and prevent viral rebound after ART interruption [14, 15]. More impressively, these studies also showed a substantial reduction in HIV DNA levels in various tissues, including lymphoid organs (spleen, lymph nodes) and even hard-to-reach sites like the brain and gut-associated lymphoid tissue (GALT), where viral reservoirs are known to persist. This reduction was often measured by quantitative PCR for HIV DNA or through *ex vivo* viral outgrowth assays, which quantify replication-competent latent virus.

Specifically, the proviral excision strategy using dual gRNAs flanking the LTRs has shown remarkable promise. Studies have reported the successful excision of large segments of the integrated provirus in humanized mice, leading to a significant decrease in total HIV DNA and intact proviral DNA, which is a more accurate measure of replication-competent virus. For instance, in models where mice were treated with ART to suppress active replication, subsequent delivery of CRISPR-Cas9 resulted in up to a 60-90% reduction in proviral DNA in various organs compared to control groups receiving placebo or only ART [16]. Critically, in some experiments, this reduction translated into prolonged suppression of viremia following ART cessation, suggesting that the gene editing intervention had a tangible impact on the size and activity of the reactivatable reservoir.

The impact of CRISPR-Cas9 is often assessed against ART alone. In models where parallel groups receive only ART, the viral reservoir size typically remains stable or declines only marginally over time, reflecting the inability of ART to clear integrated provirus. In contrast, the CRISPR-Cas9-treated groups consistently demonstrate a statistically significant reduction in reservoir markers [17, 18]. This direct comparison underscores the unique capability of gene editing to tackle the integrated provirus, a mechanism completely beyond the scope of conventional ART. Furthermore, studies have begun to explore the long-term effects of gene editing, with some showing durable reduction in reservoir size over several months, indicating the potential for a sustained therapeutic effect. The safety profile, including assessment for off-target editing, has also been a critical component of these preclinical evaluations, with ongoing efforts to minimize any unintended genomic modifications.

Comparison with Antiretroviral Therapy Alone on HIV Reservoir Reduction

The fundamental difference in the mechanism of action between CRISPR-Cas9 gene editing and antiretroviral therapy (ART) dictates their respective impacts on the HIV reservoir [19]. ART works by inhibiting various stages of the HIV replication cycle, such as reverse transcription, integration, or protease activity, thereby preventing new infections and the amplification of the viral load. However, ART does not remove or inactivate the already integrated proviral DNA that forms the latent reservoir. Consequently, while ART effectively suppresses active viral replication to undetectable levels, the integrated provirus persists, meaning the reservoir size typically remains stable or

decreases only very slowly through natural cell turnover over many years, if at all. Upon ART cessation, these latent proviruses can reactivate, leading to rapid viral rebound.
In stark contrast, CRISPR-Cas9 gene editing directly targets the integrated proviral DNA. As discussed, it can either functionally inactivate the provirus through targeted mutations or physically excise it from the host genome. This direct action on the integrated viral DNA is what fundamentally distinguishes gene editing as a potential cure strategy from ART as a chronic management tool.

When comparing the impact of CRISPR-Cas9 versus ART alone on reservoir reduction in humanized mice, the evidence overwhelmingly points to a superior efficacy for gene editing in decreasing the latent reservoir. Studies consistently show that while ART maintains viral suppression in the periphery, it has a minimal effect on the total proviral DNA or replication-competent latent virus in tissue reservoirs over typical experimental durations (weeks to months). In the same experimental settings, the addition of CRISPR-Cas9, or its administration in animals that have established latency, leads to a significant and measurable reduction in HIV DNA burden in lymphoid tissues, gut, and other reservoir sites [20, 21].
The critical metric for this comparison is the reduction in intact proviral DNA, which represents the subset of integrated viruses capable of reactivation and replication. While ART alone does not significantly impact this intact proviral DNA, CRISPR-Cas9-mediated excision strategies have demonstrated substantial reductions in this key reservoir marker in humanized mice. This difference is clinically significant because a reduction in the functional reservoir is directly correlated with the potential for long-term ART-free remission. Although complete eradication of the reservoir has not been achieved in all treated mice, the observed magnitude of reduction with CRISPR-Cas9 is a scale beyond what could be expected from prolonged ART alone within the timeframe of these studies. This underscores the transformative potential of gene editing as a direct means to tackle the most formidable barrier to an HIV cure.

Future Directions and Challenges

While the preclinical data from humanized mouse models are highly encouraging, significant challenges remain before CRISPR-Cas9 gene editing can be translated into a safe and effective cure strategy for humans.
One major hurdle is the delivery efficiency to all relevant reservoir cells in the human body. Latent HIV can reside in diverse cell types and anatomical compartments, many of which are difficult to access with current gene therapy vectors. Achieving broad and sufficient transduction of infected cells, particularly resting CD4+ T cells, which are largely quiescent, is critical. Systemic delivery of AAV vectors, while promising, may face limitations in reaching all sanctuary sites or achieving high enough transduction rates in the vast number of latently infected cells in a human. Efforts are ongoing to develop more targeted delivery systems, potentially using cell-specific targeting ligands or *ex vivo* gene editing of autologous cells, which are then reinfused.
Off-target editing remains a safety concern. While CRISPR-Cas9 is highly specific, there is a theoretical risk of unintended modifications to the host genome, which could lead to genotoxicity, oncogenesis, or other adverse effects. Rigorous preclinical validation and careful design of gRNAs to minimize off-target activity are essential. Advances in CRISPR technology, such as the development of base editors or prime editors, which offer greater precision and fewer DSBs, could further enhance safety [22].
Immune responses to Cas9 and delivery vectors could also pose a challenge. Pre-existing immunity to AAV vectors is common in humans, potentially limiting their efficacy. Similarly, the Cas9 protein itself is a bacterial protein and could elicit an immune response, leading to its clearance and limiting the duration of its activity. Strategies to mitigate these immune responses, such as using alternative Cas9 orthologs or transient delivery of Cas9 mRNA, are being explored.
Finally, ensuring the durability and completeness of reservoir reduction is crucial. Even a small number of remaining intact proviruses could lead to viral rebound. Therefore, achieving a substantial and lasting reduction, ideally to undetectable levels, across all relevant anatomical compartments is the goal. The combination of CRISPR-Cas9 with other cure strategies, such as latency reversal agents or enhanced immunotherapies (e.g., therapeutic vaccines or CAR T cells), might be necessary to achieve a truly sterilizing or functional cure. Despite these challenges, the progress in humanized mouse models provides a compelling rationale for the continued development of CRISPR-Cas9 as a potentially transformative intervention for HIV.

CONCLUSION

The persistence of the latent HIV reservoir remains the primary barrier to curing HIV infection despite the profound success of antiretroviral therapy (ART). While ART effectively suppresses viral replication, it does not eliminate the integrated provirus, necessitating lifelong treatment. CRISPR-Cas9 gene editing has emerged as a groundbreaking technology with the unprecedented potential to directly target and inactivate or excise the

integrated HIV provirus from the host genome. In humanized mouse models, a critical preclinical tool for HIV cure research, studies have consistently demonstrated that CRISPR-Cas9 gene editing significantly reduces the size of the HIV reservoir, as measured by total HIV DNA and, more importantly, intact proviral DNA, in various anatomical compartments. This effect stands in stark contrast to ART alone, which, while maintaining viral suppression, has minimal impact on the stable latent reservoir over comparable timeframes. The direct action of CRISPR-Cas9 on the proviral DNA offers a unique mechanistic advantage over ART. Although challenges related to delivery efficiency, potential off-target effects, and host immune responses to gene editing components persist, the compelling preclinical evidence from humanized mice provides a strong foundation for advancing CRISPR-Cas9 towards clinical translation as a potentially curative strategy for HIV.

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