OPEN ACCESS Freely available online

HIV: Current Research

ISSN: 2572-0805

Opinion Article

CRISPR Cas9 Gene Editing Approaches for HIV Eradication

Camila Rodríguez*

Department of Molecular Genetics and Virology, Santiago Biomedical Research Institute, Santiago, Chile

DESCRIPTION

The persistent challenge in curing HIV lies in its ability to integrate its genetic material into the host genome, forming latent reservoirs that remain hidden from immune surveillance and antiretroviral therapy (ART). While ART can effectively suppress viral replication and prolong life, it cannot eradicate the virus completely. In recent years, the emergence of CRISPR-Cas9 gene editing technology has brought renewed hope for targeting and potentially eliminating these latent reservoirs. The CRISPR-Cas9 system, derived from bacterial immune defense mechanisms, enables precise cleavage and editing of specific DNA sequences, providing a powerful tool to disrupt the proviral DNA of HIV embedded within host cells.

CRISPR-Cas9 gene editing offers a multifaceted strategy for HIV eradication. One major approach involves targeting and excising the integrated HIV provirus from the host genome. By designing guide RNAs that direct Cas9 endonuclease to conserved regions of the HIV genome such as the Long Terminal Repeats (LTRs) or essential genes like gag, pol, and env-researchers have demonstrated successful cleavage of viral DNA in various cell lines and animal models. The result is either complete excision of the provirus or significant mutational disruption that prevents functional virus replication. In preclinical studies, CRISPR-Cas9 has shown promise in reducing the HIV DNA burden in infected cells without harming host genomic integrity, a critical consideration for clinical translation.

Another promising application of CRISPR technology involves engineering HIV-resistant immune cells. By disrupting host dependency factors, such as the CCR5 co-receptor which the virus uses to enter CD4+ T cells gene editing can render immune cells resistant to infection. The landmark case of the "Berlin Patient" who was functionally cured of HIV following a bone marrow transplant from a CCR5Δ32 donor inspired researchers to mimic this resistance using CRISPR. Laboratory efforts have successfully employed CRISPR to knock out CCR5 in hematopoietic stem cells and T cells, showing sustained resistance to HIV in vitro and in humanized mouse models. These strategies aim to establish a population of genetically modified, infection-resistant immune cells that can repopulate the host and control or clear HIV infection over time.

Despite its immense potential, CRISPR-Cas9 gene editing for HIV eradication faces significant challenges. One major hurdle is efficient and targeted delivery of the gene-editing components to latently infected cells dispersed throughout the body, including in hard-to-reach reservoirs like the central nervous system, lymphoid tissues, and gastrointestinal tract. Viral vectors such as Adeno-Associated Virus (AAV) have been commonly used for in vivo delivery, but concerns about immune responses, payload limitations, and long-term safety remain. Non-viral delivery systems, such as lipid nanoparticles and electroporation, are being explored to improve precision and reduce immunogenicity.

Off-target effects, where Cas9 induces unintended mutations in the host genome, also present a serious concern. Although advances in guide RNA design, high-fidelity Cas9 variants, and rigorous screening methods have reduced the risk, absolute safety is paramount, especially when dealing with systemic, potentially irreversible gene editing in humans. Furthermore, HIV's high mutation rate poses another obstacle, as viral escape mutants can quickly arise, rendering single-guide strategies ineffective. Multiplexing CRISPR by using multiple guide RNAs targeting different conserved regions may mitigate this issue and prevent viral escape.

Ethical, regulatory, and logistical considerations also play a significant role in the future of CRISPR-based HIV therapies. The long-term impact of genome editing is still largely unknown, and public acceptance requires transparent evaluation of risks and benefits. Additionally, translating gene-editing therapies from the laboratory to clinical settings involves substantial cost, infrastructure, and expertise barriers that are especially relevant in regions heavily burdened by HIV but with limited healthcare resources.

Current research is expanding to combine CRISPR-Cas9 with other therapeutic modalities, such as latency-reversing agents (LRAs) or broadly neutralizing antibodies (bNAbs), to create synergistic cure strategies. The "shock and kill" approach, for example, involves reactivating latent HIV with LRAs and then eliminating the exposed cells using gene editing or immunotherapy. Likewise, “block and lock” strategies aim to permanently silence HIV expression through epigenetic

Correspondence to: Department of Molecular Genetics and Virology, Santiago Biomedical Research Institute, Santiago, Chile, E-mail: camila.rodriguez@sbri-cl.org

Received: 04-Mar-2025, Manuscript No. HICR-25-37647; **Editor assigned:** 06-Mar-2025, PreQC No. HICR-25-37647 (PQ); **Reviewed:** 20-Mar-2025, QC No. HICR-25-37647; **Revised:** 26-Mar-2025, Manuscript No. HICR-25-37647 (R); **Published:** 01-Apr-2025, DOI: 10.35248/2572-0805-25.10.429

Citation: Rodríguez C (2025). Advances in Long Acting Antiretroviral Therapies for HIV Management. HIV Curr Res.10:429.

modifications a goal that CRISPR might help achieve by delivering transcriptional repressors.

In conclusion, CRISPR-Cas9 gene editing represents one of the most promising frontiers in the search for a functional or sterilizing cure for HIV. Its ability to precisely target and excise integrated HIV DNA, modify host susceptibility factors, and be adapted for combination therapies offers unprecedented potential. However, the path to clinical application is still in its early stages, requiring robust validation, improved delivery systems, and a thorough understanding of long-term safety. If these challenges can be overcome, CRISPR-based strategies could revolutionize HIV treatment and bring us closer to the ultimate goal of virus eradication.