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CRISPR-Cas13 RNA-Targeting Therapeutics for Achieving Functional HIV Remission in Reservoir-Containing Tissues

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ABSTRACT

Human immunodeficiency virus (HIV) persisted as a significant global health burden, with an estimated 40.8 million people living with HIV as of 2024 despite widespread access to combination antiretroviral therapy (cART). Lifelong therapy was still required because replication-competent provirus and low-level viral transcription persisted in long-lived reservoir-containing tissues, including lymphoid organs, gut-associated lymphoid tissue, and central nervous system niches. CRISPR-Cas13, a type VI RNA-guided nuclease, has emerged as a versatile platform for programmable RNA targeting, offering the possibility of selectively degrading HIV RNA transcripts while sparing the host genome. This narrative review examined CRISPR-Cas13 RNA-targeting therapeutics in the context of achieving functional HIV remission, synthesizing current knowledge on Cas13 biology, HIV reservoir dynamics, proof-of-concept studies, and translational delivery strategies to reservoir-rich tissues. A narrative review methodology was employed, drawing on peer-reviewed literature from PubMed, Scopus, and major publishers between 2015 and 2026, with emphasis on mechanistic and preclinical studies. Emerging findings indicated that Cas13-based constructs can efficiently reduce HIV RNA levels and blunt viral gene expression, though durable impacts on reservoir size and clinical remission remain to be demonstrated. Key limitations included delivery barriers, off-target and collateral RNA cleavage, immune recognition, and scalability in diverse patient populations. CRISPR-Cas13 RNA-targeting therapeutics represented a scientifically compelling avenue for shifting HIV management from lifelong suppression to functional remission, but substantial optimization of vector design, delivery to tissue reservoirs, and long-term safety is still required before clinical translation is realistic.

Keywords: CRISPR-Cas13, RNA targeting, HIV reservoirs, Functional remission, Gene therapy.

INTRODUCTION

Human immunodeficiency virus remains a major global health challenge despite four decades of biomedical progress [1]. Recent epidemiological estimates indicate that approximately 40.8 million individuals were living with HIV worldwide in 2024, with about 1.3 million new infections annually and a significant proportion of patients residing in sub-Saharan Africa [2-6]. Combination antiretroviral therapy has transformed HIV infection from a uniformly fatal disease into a chronic manageable condition, yet cART does not eradicate the virus and must be taken continuously to prevent viral rebound. The core obstacle to cure is the persistence of long-lived viral reservoirs containing integrated provirus and transcriptionally active HIV RNA in anatomical and cellular sanctuaries such as lymph nodes, gut-associated lymphoid tissue, bone marrow, and microglial-rich niches within

the central nervous system [7-10]. Latent and low-level productive infection within these reservoirs underpins residual inflammation, non-AIDS comorbidities, and rapid viral rebound after treatment interruption, highlighting the need for strategies that directly target reservoir-derived viral RNA [11-16]. Conventional gene-editing approaches, particularly CRISPR-Cas9, have largely focused on proviral DNA excision or editing of host dependency factors, but they carry concerns about permanent off-target genomic alterations and incomplete access to transcriptionally active but non-integrated viral RNA pools. In this context, CRISPR-Cas13 systems, which exclusively recognize and cleave RNA, have attracted considerable attention as a flexible and potentially safer class of nucleic acid therapeutics. Cas13 effectors can be programmed with guide RNAs to target specific HIV transcripts, theoretically enabling potent post-transcriptional suppression of viral gene expression while avoiding direct modification of host DNA [17-19]. This narrative review synthesizes the emerging landscape of CRISPR-Cas13 RNA-targeting therapeutics with an emphasis on their potential role in achieving functional HIV remission, defined as sustained viral control and immunologic stability in the absence of continuous cART, without complete eradication of all infected cells. Section one outlines the molecular architecture and mechanistic features of Cas13 systems relevant to RNA-directed therapy, emphasizing specificity, collateral cleavage, and recent efforts to engineer high-fidelity variants. Section two reviews the biology of HIV reservoirs in lymphoid and non-lymphoid tissues, focusing on transcriptomic features and microenvironmental barriers that influence Cas13-based targeting. Section three discusses proof-of-concept studies employing Cas13 to inhibit HIV-1 infection and reduce viral RNA levels, summarizing key experimental outcomes and their implications for remission. Section four examines delivery platforms and translational considerations for distributing Cas13 constructs to reservoir-containing tissues, including viral vectors, nanoparticles, and cell-based approaches. Section five critically appraises current limitations, safety issues, and future research priorities needed to progress toward clinically meaningful functional remission [20-27]. The purpose of this review is to provide medical biochemistry and translational research communities with a concise yet conceptually integrated appraisal of CRISPR-Cas13 RNA-targeting therapeutics in HIV, delineate realistic opportunities and barriers for achieving functional remission in reservoir-containing tissues, and identify avenues where focused mechanistic and preclinical work can accelerate rational clinical development.

CRISPR-Cas13 Biology and Mechanism Relevant to HIV RNA Targeting

Type VI CRISPR-Cas13 systems are single-effector, RNA-guided endonucleases originally characterized in prokaryotic adaptive immunity against RNA phages and mobile genetic elements. Cas13 proteins form complexes with CRISPR-derived guide RNAs that direct binding to complementary RNA targets, triggering conformational changes that activate HEPN-domain RNase activity. Once engaged, Cas13 can cleave the bound target and, in some contexts, collateral non-target RNAs, producing robust transcript depletion [6, 7,27].

From a therapeutic perspective, the central advantages of Cas13 include its exclusive RNA specificity, programmability via short guide sequences, and capability to modulate gene expression without permanent editing of genomic DNA [8, 9]. Cas13 has been adapted for applications encompassing mRNA knockdown, circular RNA degradation, noncoding RNA modulation, and RNA editing through fusion with deaminases, demonstrating broad utility in research and potential clinical contexts. Importantly, recent structural and biochemical work has delineated features governing self–non-self-discrimination, guide design rules, and factors influencing collateral activity, enabling more rational engineering of therapeutic variants [10]. For HIV, Cas13-guided constructs can be directed against conserved regions of gag, pol, env, or regulatory transcripts such as tat and rev, with the aim of destabilizing viral RNA and blunting production of structural proteins and enzymes required for productive infection. Cas13d and Cas13a subtypes have been particularly attractive because of their compact size and robust activity in mammalian cells, enabling packaging into standard gene therapy vectors. Nevertheless, the risk of collateral RNA degradation at high effector expression levels remains a key concern, especially in reservoir-containing tissues where precise control of host transcriptomes is essential for tissue homeostasis. Strategies such as low-copy expression, high-fidelity Cas13 variants with reduced collateral activity, and careful titration of guide abundance are being explored to balance antiviral potency with acceptable safety [11]. Collectively, Cas13 biology provides a mechanistically coherent foundation for RNA-targeting HIV therapeutics but underscores the need for meticulous optimization of guide architecture and effector variants to minimize unintended impacts on host cell RNA networks [12].

HIV Reservoir Biology in Tissues: Implications for RNA-Targeting Strategies

HIV reservoirs comprise heterogeneous populations of infected cells that persist despite suppressive cART, including resting memory CD4 T cells, follicular helper T cells, macrophages, and microglia, distributed across lymph nodes, spleen, gut-associated lymphoid tissue, bone marrow, and central nervous system compartments. These reservoirs are characterized by integrated proviral DNA and episodic transcription of viral RNA, often in environments with restricted drug penetration, altered immune surveillance, and complex stromal interactions [3]. From the standpoint of RNA-targeting therapy, reservoir biology poses several challenges and opportunities. Persistent but low-level HIV RNA transcription in lymphoid and mucosal tissues creates a moving target whose abundance may fluctuate with immune activation, co-infections, and local cytokine milieus [13]. The microarchitecture of lymphoid follicles and gut tissue, with dense cellular aggregates and extracellular matrix barriers, can hinder vector diffusion and uptake, complicating delivery of Cas13 constructs. Additionally, tissue-resident macrophages and microglia in brain and peripheral tissues exhibit distinct transcriptional programs and innate immune sensitivity, influencing both viral persistence and responses to foreign nucleic acid therapeutics [14]. At the same time, the fact that these reservoirs rely on ongoing transcription to sustain viral fitness provides a mechanistic rationale for RNA-directed interventions. Cas13 effectors, if successfully deployed to reservoir-containing tissues, could degrade nascent viral transcripts before translation, attenuating cell-to-cell spread and diminishing immunopathogenic stimulus from viral proteins. Conceptually, sustained suppression of reservoir-derived RNA might convert HIV infection into a state of functional remission, where viral genomes remain but are transcriptionally silent or rapidly neutralized at the RNA level, reducing the likelihood of systemic rebound upon cART withdrawal. However, achieving this state will require precise targeting of tissue-specific reservoir compartments, durable expression or repeated delivery of Cas13 constructs, and integration with existing or novel latency-reversing or immunomodulatory approaches [15].

Thus, the spatial and cellular complexity of HIV reservoirs frames the biophysical, immunologic, and pharmacologic constraints within which Cas13-based therapies must operate, while simultaneously focusing attention on RNA expression as a logical vulnerability for therapeutic exploitation [3].

Evidence for Cas13-Mediated HIV RNA Suppression and Prospects for Functional Remission

Experimental support for Cas13-mediated HIV suppression has emerged from in vitro models demonstrating targeted RNA degradation and reduced viral replication [16]. A seminal study repurposed CRISPR-Cas13a to inhibit HIV-1 infection by directing guide RNAs against conserved viral RNA regions, which led to diminished HIV gene expression and reduced production of infectious virions in human cell lines. These findings illustrated that Cas13 can be harnessed to interfere with HIV at the transcript level and provided proof-of-principle that programmable RNA targeting can translate into measurable antiviral effects [11]. Subsequent work has expanded Cas13 applications to broader RNA therapeutic contexts, demonstrating potent knockdown of various endogenous transcripts and indicating that similar architectures could be adapted for HIV targets [17]. Reviews of Cas13-based technologies consistently emphasize the versatility of RNA-centric approaches, including modulation of splicing, RNA editing, and noncoding RNA regulation, all of which may be relevant to complex HIV latency and reservoir phenotypes. Furthermore, emerging analyses of high-fidelity Cas13 variants suggest that refined effector design can reduce collateral cleavage while maintaining robust on-target activity, thereby improving the therapeutic window for antiviral applications [5]. Despite these advances, direct evidence that Cas13 interventions can meaningfully diminish reservoir size or sustain functional remission in vivo remains preliminary [18]. Most studies have been conducted in cell culture systems or limited animal models that do not fully recapitulate the anatomical complexity and long-term dynamics of human HIV reservoirs. Moreover, metrics such as transient reductions in viral RNA or delayed rebound in experimental systems do not yet equate to durable remission in patients. Achieving functional remission will likely require multi-pronged regimens in which Cas13-based RNA targeting is combined with latency reversal, immune enhancement, or complementary genome-editing approaches aimed at proviral DNA [12]. In summary, existing evidence supports the feasibility of Cas13-mediated HIV RNA suppression but underscores the gap between successful in vitro knockdown and clinically relevant reservoir control. Carefully designed preclinical models that integrate tissue reservoir biology and longitudinal outcome measures will be essential to evaluate whether Cas13 therapies can drive the system toward stable functional remission [11].

Delivery of Cas13 Therapeutics to Reservoir-Containing Tissues

Effective deployment of CRISPR-Cas13 therapeutics hinges on overcoming the formidable hurdle of delivering effector constructs to the diverse reservoir-containing tissues in which HIV persists. Several delivery modalities have been explored or proposed for RNA-targeting gene therapies, including adeno-associated viral (AAV) vectors, lentiviral vectors, lipid nanoparticles, and engineered cell-based vehicles [4].

AAV vectors offer stable transduction and tissue tropism profiles that can be tuned by capsid engineering, and their established use in human gene therapy trials makes them an appealing platform for Cas13 delivery [19]. However, pre-existing immunity, limited packaging capacity, and concerns about long-term expression of nuclease effectors in sensitive tissues must be carefully addressed. Lentiviral vectors enable integration in dividing cells and have been widely used in ex vivo manipulation of hematopoietic stem cells and T cells, which could support autologous cell therapies engineered to express Cas13 and traffic to lymphoid reservoirs. Lipid nanoparticles and other non-viral systems provide transient expression and may reduce immunogenicity, but achieving sufficient delivery efficiency and tissue penetration in vivo is challenging, especially in gut and central nervous system compartments [6]. Recent mechanistic studies of Cas13d delivery have highlighted the importance of using low-copy expression systems to minimize collateral RNA degradation, as high-level expression can trigger unintended global transcriptome perturbations. High-fidelity Cas13 variants engineered to reduce collateral activity while preserving on-target knockdown offer further optimization options. Additionally, strategies that exploit receptor-mediated uptake or homing of engineered immune cells to lymphoid follicles and mucosal tissues may improve localization of Cas13 constructs to reservoir-rich niches [15]. Ultimately, no single delivery approach is likely to suffice across all reservoir compartments, and rational combinations or sequential strategies may be necessary. Robust pharmacokinetic and pharmacodynamic profiling, coupled with advanced imaging and single-cell transcriptomics, will be essential to validate that Cas13 therapeutics reach relevant cells, achieve adequate RNA knockdown, and maintain acceptable safety profiles over clinically meaningful time frames [5].

Challenges, Safety Considerations, and Future Directions

While CRISPR-Cas13-based RNA therapeutics are conceptually attractive for HIV remission, several challenges and safety considerations must be critically confronted. First, off-target and collateral RNA cleavage remain central concerns; high effector expression or suboptimal guide design can lead to unintended degradation of host transcripts, with potential cytotoxic or immunomodulatory consequences [20, 21]. Second, innate and adaptive immune responses against Cas proteins, guide RNAs, or delivery vectors may limit persistence and efficacy, particularly in heavily inflamed or immunologically primed HIV-infected tissues. Third, viral escape through mutation of targeted RNA sequences is a plausible risk, necessitating multiplexed guide strategies directed at highly conserved regions of the HIV genome [4]. From a translational perspective, manufacturing complexity, cost, and equitable access are non-trivial barriers to deploying advanced gene therapies in global HIV populations, many of whom live in resource-limited settings. Ethical considerations related to long-term expression of gene-editing effectors, potential germline exposure, and governance of high-tech cures must also be carefully navigated. Nevertheless, ongoing structural and mechanistic studies of Cas13 are steadily refining our understanding of effector behavior, guiding design of safer, more precise variants. Parallel development of delivery platforms and integration with systems biology tools is likely to accelerate rational optimization [6]. Future research priorities include systematic mapping of HIV RNA vulnerabilities across reservoir compartments, comparative evaluation of Cas13 subtypes and engineered variants in relevant preclinical models, development of multiplexed guide libraries to preempt viral escape, and rigorous long-term safety assessment in animal systems. Importantly, Cas13-based strategies should be investigated not only as stand-alone interventions but as components of combination regimens with latency-reversing agents, immune checkpoint modulators, therapeutic vaccines, or Cas9/Cas12-based DNA targeting approaches. Such integrative programmes may offer the best chance of translating molecular promise into clinically durable functional remission [15].

CONCLUSION

CRISPR-Cas13 RNA-targeting therapeutics occupy an intriguing niche in the evolving landscape of HIV cure research, providing a programmable, RNA-focused modality that complements DNA-directed editing and conventional pharmacologic suppression. Mechanistic studies have demonstrated that Cas13 effectors can be engineered to selectively degrade HIV transcripts and attenuate viral gene expression, while advances in effector

design and delivery strategies are beginning to address key challenges related to specificity, collateral activity, and tissue targeting. Nevertheless, translation from in vitro proof-of-concept to clinically meaningful functional remission in reservoir-containing tissues remains an ambitious goal. The anatomical complexity of reservoirs, risks of off-target RNA perturbation, immune barriers, and potential for viral escape collectively underscore the need for cautious, methodical progression through preclinical and early-phase clinical studies. If these obstacles can be surmounted, Cas13-based RNA targeting may one day enable durable suppression of reservoir-derived viral transcription, reducing or even eliminating the need for lifelong cART and shifting HIV management toward a state of sustained functional remission. Realizing this vision will require sustained interdisciplinary collaboration among molecular biochemists, virologists, immunologists, clinicians, and implementation scientists to ensure that sophisticated gene therapies are safe, effective, and globally accessible. Focused, well-controlled preclinical studies integrating Cas13-based RNA targeting with complementary latency-modulating and immune-enhancing strategies should be prioritized to rigorously evaluate their capacity to achieve functional HIV remission in reservoir-containing tissues.

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