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CRISPR-Cas9 Gene Editing to Achieve HIV Cure: Current Progress and Barriers

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ABSTRACT

Human immunodeficiency virus type 1 persisted as a global health challenge affecting approximately 39 million individuals worldwide, with current antiretroviral therapy requiring lifelong adherence while failing to eliminate latent viral reservoirs. CRISPR-Cas9 represented a revolutionary gene editing technology capable of precise genomic modifications, offering unprecedented opportunities to disrupt integrated proviral DNA and confer resistance to viral entry through targeted modification of host cellular factors. This review critically examined the application of CRISPR-Cas9 gene editing systems toward achieving functional cure or eradication of human immunodeficiency virus infection, evaluating molecular strategies, preclinical evidence, clinical translation efforts, and obstacles limiting therapeutic implementation. A comprehensive synthesis of mechanistic studies, preclinical models, early phase clinical trials, and theoretical frameworks published through early 2025 addressing CRISPR-Cas9 targeting of integrated provirus, CCR5 coreceptor modification, and combinatorial approaches was utilized in writing this review. CRISPR-Cas9 systems demonstrated capacity to excise integrated proviral sequences from infected cell genomes, disrupt CCR5 coreceptor expression to prevent viral entry, and target conserved viral regulatory elements across diverse human immunodeficiency virus subtypes in cellular and animal models. However, substantial barriers persisted including incomplete elimination of latent reservoirs, off target genomic modifications, inefficient delivery to anatomical sanctuary sites, immune responses against Cas9 protein, viral escape through sequence variation, and technical challenges in achieving therapeutically relevant editing frequencies in vivo. While CRISPR-Cas9 technologies offered compelling theoretical frameworks for human immunodeficiency virus cure, translation from preclinical promise to clinical reality required innovations in delivery systems, editing efficiency, safety profiles, and strategies addressing viral reservoir heterogeneity.

Keywords: CRISPR-Cas9, Human immunodeficiency virus cure, Proviral excision, CCR5 modification, Gene therapy.

INTRODUCTION

CRISPR-Cas9 constitutes a bacterial adaptive immune system repurposed as a programmable genome editing platform that enables precise modification of DNA sequences in eukaryotic cells [1, 2]. The system comprises two essential components: the Cas9 endonuclease enzyme derived from Streptococcus pyogenes or related bacterial species, and a single guide RNA molecule that directs the Cas9 protein to complementary target sequences through Watson-Crick base pairing [3]. Upon recognition of a target site adjacent to a protospacer adjacent motif sequence, Cas9 induces a double strand break that is subsequently repaired through either nonhomologous end joining, resulting in insertions or deletions, or homology directed repair when a DNA template is provided. This precision targeting capacity revolutionized biomedical research and sparked intensive investigation into therapeutic applications across genetic diseases, cancer, and infectious diseases. The relative simplicity of CRISPR-Cas9 compared with earlier genome editing platforms such as zinc finger nucleases and transcription activator like effector nucleases has democratized gene editing and accelerated translational research timelines [4].

Human immunodeficiency virus type 1 establishes persistent infection through integration of reverse transcribed viral DNA into host cell chromosomes, creating stable proviral reservoirs that persist despite suppressive antiretroviral therapy [5]. Current treatment regimens effectively suppress viral replication and prevent disease progression but cannot eliminate integrated provirus from long lived memory CD4 positive T cells, macrophages, and other cellular reservoirs [6]. Treatment interruption uniformly results in viral rebound within weeks as latent provirus reactivates, necessitating lifelong therapy with attendant challenges including adherence burden, cumulative toxicities, drug resistance emergence, and healthcare costs. The concept of human immunodeficiency virus cure encompasses two distinct goals: sterilizing cure involving complete viral eradication, and functional cure characterized by sustained viral remission without antiretroviral therapy despite persistent low-level reservoirs. CRISPR-Cas9 technologies offer potential pathways to both cure modalities through direct excision of integrated provirus or through modification of host factors essential for viral replication, mimicking naturally occurring CCR5 delta 32 mutations that confer resistance to CCR5 tropic virus [7]. The objective of this review is to critically evaluate current progress in applying CRISPR-Cas9 gene editing systems toward achieving human immunodeficiency virus cure, examining molecular strategies targeting viral and host genomes, assessing preclinical and clinical evidence, and identifying major barriers impeding translation from laboratory models to effective clinical therapies.

Molecular Strategies for CRISPR-Cas9 Mediated HIV Targeting

CRISPR-Cas9 approaches to human immunodeficiency virus cure employ three principal molecular strategies: direct excision of integrated proviral DNA, disruption of essential host dependency factors, and targeting conserved viral regulatory sequences [8]. Proviral excision strategies design guide RNAs targeting sequences flanking integrated provirus, typically within the long terminal repeat regions that contain regulatory elements essential for viral transcription. Simultaneous cleavage at both 5 prime and 3 prime long terminal repeats enables removal of intervening proviral sequences, potentially eliminating replication competent virus from infected cells [9]. In vitro studies demonstrate successful excision from chronically infected cell lines and patient derived primary cells, with polymerase chain reaction and sequencing confirmation of precise deletions. However, the efficiency varies substantially depending on chromatin accessibility, integration site characteristics, and guide RNA design parameters. Furthermore, incomplete excision leaving residual long terminal repeat sequences or imprecise repair generating hybrid junctions may retain pathogenic potential or create novel genomic alterations.

Host factor modification strategies focus primarily on CCR5, the chemokine coreceptor essential for entry of CCR5 tropic viral strains that predominate during early infection [10]. CRISPR-Cas9 mediated CCR5 disruption mimics naturally occurring CCR5 delta 32 deletion mutations prevalent in European populations that confer resistance to human immunodeficiency virus infection without apparent adverse health consequences. Guide RNAs targeting CCR5 exons induce frameshift mutations that abolish functional receptor expression on cell surfaces [11]. Additional host factors including CXCR4 coreceptor and integrated cofactors represent alternative targets, though CCR5 remains most extensively studied given established safety profile of natural deletions [12].

Targeting conserved viral regulatory elements offers advantages of potentially affecting multiple integrated proviruses regardless of integration site while avoiding extensive host genome modification. Guide RNAs directed against essential regions within Gag, Pol, Env, or regulatory genes such as Tat and Rev can disable viral replication capacity even if provirus remains integrated [13, 14]. The high mutation rate of human immunodeficiency virus presents challenges, as sequence variation may prevent guide RNA recognition or enable viral escape. Computational approaches identify highly conserved sequences across diverse viral subtypes and within patient quasispecies populations to design pangenotypic guide RNAs. Multiplexed strategies employing multiple guide RNAs targeting distinct viral sequences simultaneously reduce escape probability while increasing overall editing efficiency. The integration of these molecular strategies into clinical applications requires optimization of editing parameters, comprehensive off target assessment, and consideration of viral reservoir heterogeneity that characterizes chronic infection.

Preclinical Evidence and Animal Model Studies

Preclinical validation of CRISPR-Cas9 strategies for human immunodeficiency virus cure has progressed through in vitro cellular systems, humanized mouse models, and nonhuman primate studies, each providing distinct insights while presenting inherent limitations [15]. Initial proof of concept studies in transformed cell lines chronically infected with laboratory adapted viral strains demonstrated feasibility of proviral excision, with subsequent refinement in primary CD4 positive T cells from virally suppressed patients. These studies established that CRISPR-Cas9 could locate and cleave integrated provirus within complex genomic contexts, though editing efficiencies varied from less than 5% to over 50% depending on delivery method, guide RNA design, and cellular activation state. Critically, successful proviral excision in a fraction of cells does not translate directly to therapeutic benefit, as residual infected cells maintain replication capacity. Quantitative viral outgrowth assays demonstrate modest

reductions in replication competent reservoir size following CRISPR treatment, underscoring the challenge of achieving near complete reservoir elimination required for functional cure.

Humanized mouse models, generated by engrafting human hematopoietic cells into immunodeficient mice, enable assessment of CRISPR-Cas9 efficacy in vivo while controlling viral strain, infection timing, and treatment interventions [16]. Studies employing adeno associated viral vectors or lentiviral vectors to deliver CRISPR components demonstrate editing in human cells residing in murine tissues, with some investigations reporting reduced viral loads or delayed viral rebound following antiretroviral therapy interruption. However, humanized mice incompletely recapitulate human immune system complexity, lack fully developed lymphoid tissues that serve as major reservoir sites, and exhibit abbreviated experimental timelines compared with decades long human infection. Furthermore, the efficiency of CRISPR delivery to anatomically diverse reservoir sites including central nervous system, gastrointestinal lymphoid tissue, and genital tract remains inadequately modeled. Nonhuman primate studies using simian immunodeficiency virus or simian human immunodeficiency virus chimeras provide more physiologically relevant infection models but face challenges including species specific differences in Cas9 immunogenicity and limited availability constraining experimental scale.

Recent advances integrate CRISPR-Cas9 with latency reversal agents in shock and kill strategies, where latency reversing agents induce proviral transcription to expose latently infected cells while CRISPR targets actively transcribing virus [17]. Combination approaches also explore simultaneous targeting of provirus and host factors to achieve synergistic effects. Animal studies incorporating these combinatorial strategies show enhanced reservoir reduction compared with single modality interventions, suggesting that multicomponent approaches may prove necessary for clinically meaningful cure. Nonetheless, preclinical models consistently reveal that achieving therapeutically relevant editing frequencies across heterogeneous reservoir populations remains a formidable challenge requiring continued innovation in delivery technologies and editing system optimization.

Clinical Translation and Early Phase Human Studies

Translation of CRISPR-Cas9 technologies from preclinical models to human clinical trials for human immunodeficiency virus cure has advanced cautiously, with initial studies focusing on safety assessment and proof of concept rather than efficacy endpoints. The first clinical application involved ex vivo CRISPR-Cas9 modification of autologous CD4 positive T cells targeting CCR5, administered to a small cohort of virally suppressed patients [18]. Results demonstrated feasibility of manufacturing edited cell products, acceptable safety profiles without serious adverse events attributed to gene editing, and successful engraftment of modified cells. However, edited cells comprised only a small fraction of circulating CD4 populations, typically less than 10%, and no participants achieved sustained virologic control following antiretroviral therapy interruption. These findings highlighted the substantial gap between achievable editing frequencies and the threshold required for clinical benefit, estimated to require greater than 50% of target cells to confer meaningful viral suppression.

Subsequent clinical efforts have explored CRISPR-Cas9 modification of hematopoietic stem and progenitor cells, hypothesizing that editing these multipotent precursors would generate durable populations of virus resistant immune cells through ongoing differentiation and self renewal [19]. Early phase trials enrolling small numbers of patients undergoing autologous stem cell transplantation for concurrent hematologic malignancies have incorporated CCR5 targeted CRISPR editing into conditioning regimens. Preliminary reports indicate successful engraftment of edited stem cells with long term persistence of CCR5 disrupted lymphocyte populations, though again at frequencies insufficient to mediate virologic control. One participant with acute lymphoblastic leukemia and concurrent human immunodeficiency virus infection achieved prolonged remission of malignancy while maintaining suppressed viral loads on antiretroviral therapy, demonstrating feasibility but not establishing cure. Intensive monitoring for off target effects, chromosomal abnormalities, and clonal expansions has thus far revealed reassuring safety signals, though longer follow up in larger cohorts remains essential.

The regulatory landscape governing CRISPR-Cas9 clinical trials emphasizes rigorous preclinical safety data, comprehensive off target assessment, and conservative dose escalation protocols [20]. Manufacturing challenges include production scalability, quality control ensuring consistent editing outcomes, and cost structures that may limit accessibility even if clinical efficacy is established. Patient selection criteria for early trials typically require virologic suppression, preserved immune function, and absence of drug resistant viral variants, potentially limiting generalizability to broader patient populations including those with treatment failure or advanced immunodeficiency. Future clinical development will likely require innovations in delivery systems capable of efficiently targeting reservoir cells in vivo rather than relying on ex vivo cell modification, as well as combination strategies integrating CRISPR with latency reversal, therapeutic vaccination, or broadly neutralizing antibodies to achieve sufficient reservoir reduction for functional cure.

Technical Barriers and Off Target Considerations

Substantial technical barriers impede the path from CRISPR-Cas9 proof of concept to clinically effective human immunodeficiency virus cure strategies, with delivery efficiency and off target effects representing primary concerns.

Delivery of CRISPR components to relevant cell populations across anatomically distributed viral reservoirs presents formidable challenges, as no current vector system achieves both broad tissue distribution and high transduction efficiency in nondividing cells characteristic of latently infected memory T cells [21, 22]. Adeno associated viral vectors demonstrate favorable safety profiles and clinical track records but face cargo size constraints limiting packaging of large Cas9 genes and multiple guide RNAs, restricted tropism for certain cell types, and pre existing neutralizing antibodies in substantial proportions of human populations. Lentiviral vectors accommodate larger genetic payloads and efficiently transduce hematopoietic cells but carry theoretical integration risks and typically require ex vivo modification protocols. Lipid nanoparticles, successfully deployed for messenger RNA vaccine delivery, offer potential for in vivo CRISPR delivery as ribonucleoprotein complexes but demonstrate limited lymphoid tissue penetration and rapid clearance kinetics.

Off target cleavage at genomic sites sharing partial sequence homology with intended targets poses significant safety risks including chromosomal translocations, tumor suppressor disruption, and oncogene activation [23]. Whole genome sequencing studies of CRISPR treated cells reveal off target events at frequencies ranging from undetectable to several percent depending on guide RNA design, Cas9 variant employed, and delivery method. While most off target sites occur in noncoding regions with uncertain functional consequences, rare events affecting critical genes could confer selective growth advantages driving clonal expansion, a particular concern in long lived hematopoietic stem cells. Strategies to mitigate off target risks include high fidelity Cas9 variants with enhanced specificity, truncated guide RNAs reducing promiscuous binding, and bioinformatic tools for comprehensive off target prediction and empirical validation. Additionally, delivery of CRISPR components as ribonucleoprotein complexes rather than expression plasmids reduces exposure duration and consequently off target probability, though at the cost of editing efficiency.

Immunogenicity of bacterial derived Cas9 protein represents an underappreciated barrier, with studies demonstrating pre existing humoral and cellular immunity against Streptococcus pyogenes Cas9 in substantial proportions of healthy individuals due to prior bacterial exposure [24]. Adaptive immune responses against Cas9 may eliminate edited cells, reduce editing efficiency upon repeated administration, and potentially cause inflammatory toxicities. Alternative Cas orthologs from bacterial species with limited human exposure, or engineered Cas variants with reduced immunogenic epitopes, may mitigate these concerns. The high mutation rate of human immunodeficiency virus enables viral escape from CRISPR targeting through sequence variation, particularly when single guide RNAs target variable genomic regions. Multiplexed approaches targeting multiple conserved sequences reduce but do not eliminate escape potential. These technical barriers collectively underscore the substantial innovation required to transform CRISPR-Cas9 from a promising laboratory tool into a safe and effective clinical cure strategy.

Future Directions and Path Forward to Clinical Implementation

Achieving clinically effective CRISPR-Cas9 based human immunodeficiency virus cure requires coordinated advances across multiple domains including delivery technology, editing system optimization, reservoir characterization, and regulatory pathways [25, 26]. Next generation delivery systems under development include engineered viral vectors with modified tropism targeting specific immune cell subsets, targeted nanoparticles decorated with ligands recognizing CD4 or chemokine receptors, and cell penetrating peptides facilitating direct cytoplasmic delivery of ribonucleoprotein complexes. Innovations such as virus like particles pseudotyped with envelope proteins conferring lymphotropism or exosome based delivery leveraging natural cellular communication pathways may overcome current vector limitations. Achieving therapeutically relevant biodistribution to sanctuary sites including central nervous system, lymph nodes, and gastrointestinal mucosa remains critical, potentially requiring multimodal delivery strategies tailored to distinct anatomical compartments.

Editing system refinements focus on developing compact Cas nucleases compatible with adeno associated viral packaging, base editors enabling single nucleotide modifications without double strand breaks, and prime editors facilitating precise insertions or replacements [27]. These advanced editing modalities may enhance safety profiles by avoiding double strand break associated risks while maintaining therapeutic efficacy. Multiplexed strategies targeting provirus and multiple host dependency factors simultaneously could provide redundant mechanisms of viral control, reducing reliance on near complete reservoir elimination. Combination approaches integrating CRISPR-Cas9 with broadly neutralizing antibodies, therapeutic vaccines, latency reversal agents, or immune checkpoint inhibitors represent rational strategies to address reservoir heterogeneity and enhance cure probability [28]. Computational modeling and systems biology approaches may identify optimal combination regimens and predict individual patient responses based on reservoir characteristics and immunologic parameters.

Comprehensive reservoir characterization using advanced technologies including single cell genomics, spatial transcriptomics, and intact proviral DNA assays will inform rational targeting strategies and enable precise monitoring of cure interventions [29]. Biomarker development to predict treatment response and identify residual replication competent reservoir persistence remains essential for clinical trial design and regulatory approval

pathways. Ethical considerations include ensuring equitable access to expensive gene therapies, informed consent processes clearly communicating uncertain efficacy balanced against potential risks, and prioritization frameworks for patient selection given limited initial treatment capacity [30]. Regulatory agencies require extensive long term safety data, particularly regarding clonal dynamics of edited hematopoietic cells and delayed off target consequences. The path forward necessitates sustained investment in foundational research, iterative clinical trial designs incorporating adaptive elements, and collaborative frameworks integrating academic researchers, biotechnology companies, regulatory agencies, and patient communities to transform CRISPR-Cas9 from promising concept to realized cure strategy.

CONCLUSION

CRISPR-Cas9 gene editing technologies offer theoretically compelling approaches to human immunodeficiency virus cure through direct proviral excision, host factor modification conferring viral resistance, or disruption of essential viral regulatory elements. Preclinical studies establish proof of concept that CRISPR systems can locate and modify integrated provirus in relevant cellular models, while early clinical trials demonstrate manufacturing feasibility and acceptable short term safety profiles. However, substantial barriers separate current capabilities from clinically effective cure strategies, including inefficient delivery to anatomically distributed reservoir cells, off target genomic modifications with uncertain long term consequences, immunogenicity of bacterial Cas9 proteins, and viral escape through sequence variation. Editing frequencies achieved in clinical studies remain far below thresholds estimated to confer meaningful virologic control, with no participant achieving sustained remission following antiretroviral therapy interruption. The complexity of viral reservoirs spanning multiple cell types, tissue compartments, and activation states compounds therapeutic challenges requiring comprehensive targeting strategies. Integration of CRISPR-Cas9 with complementary cure modalities including latency reversal, therapeutic vaccination, and broadly neutralizing antibodies may prove necessary to achieve reservoir elimination or durable remission. While evidence quality from controlled preclinical studies is high, clinical translation remains at early stages with limited efficacy data and incomplete long term safety assessment. The revolutionary potential of CRISPR-Cas9 for human immunodeficiency virus cure remains unrealized but represents an active research frontier with continued innovation in delivery systems, editing platforms, and combination strategies positioning the field for potential breakthroughs. Prioritize development of in vivo CRISPR delivery systems achieving high efficiency lymphoid tissue penetration combined with multiplexed targeting strategies, supported by rigorous off target assessment and long term clonal tracking in well designed clinical trials with clearly defined virologic and immunologic endpoints.

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