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HIV Cure Strategies: A Focused Review

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Abstract
The persistence of latent HIV reservoirs remains the primary barrier to achieving HIV cure. Current antiretroviral therapy (ART) suppresses viral replication but cannot eliminate these reservoirs, necessitating innovative strategies to either annihilate or control the virus. This review discusses five key HIV cure strategies: (1) shock-and-kill, which aims to reactivate latent HIV for immune clearance; (2) block-and-lock, which seeks to silence viral transcription; (3) gene editing and stem cell transplantation, which offers precise removal or resistance to HIV; (4) broadly neutralizing antibodies (bNAbs) and immune-based therapies, which enhance immune responses against the virus; and (5) immune modulation and targeted activation, including toll-like receptor (TLR) agonists, HIV-specific antigens, and immune checkpoint blockade. While each strategy shows promise, challenges such as reservoir heterogeneity, immune evasion, and scalability must be addressed. Combining these approaches may offer the best path toward a functional or sterilizing cure for HIV.

Keywords: HIV Cure Strategies, Latent Reservoirs, Antiretroviral Therapy (ART)

Introduction

The quest for HIV cure has given rise to many strategies aimed at either eliminating the latent viral reservoir or achieving long-term viral suppression without the need for antiretroviral therapy (ART). Each strategy targets different aspects of viral persistence, from reactivating latent HIV to enhancing immune clearance or silencing viral transcription. These strategies can be broadly grouped under two main approaches: sterilizing cure, which seeks to completely eradicate HIV from the body, and a functional cure, where the virus remains in the body, but its activity is well controlled without ART. Although significant progress has been made, hurdles such as immune exhaustion, incomplete reservoir targeting, and scalability must be overcome to achieve a cure (Chou et al., 2024; Ismail et al., 2021). This paper discusses some of the most promising strategies currently under investigation.

Methods

This review is based on a focused assessment of two major articles on HIV cure topics that appeared in the last five years: Chou et al. (2024) and Ismail et al. (2021). From these articles, both HIV persistence, latency mechanisms and cure treatment plans were thoroughly reviewed. The data analysis focused on identifying the mechanisms, strengths, and limitations of each strategy. Special attention was given to

preclinical and clinical findings, as well as the potential for combining strategies to enhance efficacy. This review is based on publicly available data and does not involve human participants, so ethical approval was not required.

Results

HIV Cure Strategies

1. Shock-and-Kill (Latency Reversal and Immune Clearance)

The "shock-and-kill" strategy seeks to reactivate latent HIV proviruses in reservoir cells, making them visible to the immune system or susceptible to viral cytopathic effects, as ART prevents new infections simultaneously. Latency-reversing agents (LRAs), such as protein kinase C (PKC), agonists and histone deacetylase inhibitors (HDACis), have been proven to "kick" the virus out of latency. For example, HDACis like vorinostat and romidepsin have shown some success in reactivating latent HIV in clinical trials, but they are unable to induce sufficient viral protein expression for immune recognition (Chou et al., 2024). PKC agonists, such as bryostatin-1 analogs, have demonstrated stronger latency reversal in preclinical models but are constrained clinically due to challenges related to toxicity and incomplete reservoir targeting (Ismail et al., 2021). Regardless of these limitations, combining LRAs with immune-boosting therapies, such as broadly neutralizing antibodies (bNAbs) or therapeutic vaccines, holds potential for improving the "kill" phase of this strategy.

Another groundbreaking and hopeful method in HIV cure studies involves the use of HIV-specific antigens, such as virus-like particles (VLPs), to selectively reactivate latently infected cells. VLPs mimic the structure of HIV and can stimulate immune responses without causing infection. Preclinical studies show that VLPs can cause strong latency reversal in cells with HIV-specific T-cell receptors (Chou et al., 2024). This targeted approach reduces off-target effects and could be a safer alternative to broad-acting LRAs. However, the difficulty remains in ensuring that all latent cells are reactivated and effectively cleared, as even the smallest residual reservoir can lead to viral rebound (Ismail et al., 2021).

2. Block-and-Lock (Permanent Latency)

The "block-and-lock" strategy in contrast to the shock-and-kill approach, seeks to permanently lock or silence HIV proviruses, to prevent their reactivation and reduce the risk of viral rebound. This strategy draws on small molecules and epigenetic modifiers to enforce deep latency. For instance, didehydro-cortistatin A (dCA), a Tat inhibitor, has shown promise in preclinical studies by blocking HIV transcription and inducing repressive chromatin states at the viral promoter (Chou et al., 2024). In humanized mouse models, dCA treatment delayed viral rebound after ART interruption, suggesting its potential as a functional therapeutic cure. Similarly, inhibitors of the JAK-STAT pathway, such as ruxolitinib, have been investigated for their ability to suppress HIV transcription by reducing T-cell activation (Ismail et al., 2021). Long-acting formulations of these inhibitors will be necessary to ensure sustained suppression of viral transcription.

The block-and-lock approach is appealing because it does not require the complete elimination of the reservoir, which is a significant hurdle for the shock-and-kill strategy. While block-and-lock may not eliminate HIV entirely, it could remarkably reduce chronic inflammation and immune activation associated with residual viral expression, improving the quality of life for people living with HIV (Chou et al., 2024). However, achieving durable and universal proviral silencing remains a challenge.

3. Gene Editing and Stem Cell Transplantation

CRISPR-Cas9, a gene editing technology, offers a precise way to target and excise integrated HIV provi-

ruses from the host genome. Recent studies have shown the feasibility of using CRISPR to disrupt the HIV long terminal repeat (LTR) or excise viral DNA from infected cells (Chou et al., 2024). This strategy holds much promise despite challenges related to delivery efficiency, the need to edit every latently infected cell, and off-target effects.

Stem cell transplantation on the other hand has provided proof-of-concept for a sterilizing cure in a few individuals, such as the "Berlin" and "London" patients, who received CCR5Δ32/Δ32 donor cells. The CCR5Δ32 mutation confers resistance to HIV infection, and the transplant process eliminates the existing reservoir (Ismail et al., 2021). Unfortunately, this method cannot be scaled or generalized because of the high risks, costs, and the small pool of suitable donors available. Researchers have recently resorted to gene therapy aimed at engineering a patient's stem cells to have the CCR5Δ32 mutation, a safer and more available solution (Chou et al., 2024).

4. Broadly Neutralizing Antibodies (bNAbs) and Immune-Based Therapies

Broadly neutralizing antibodies (bNAbs) have emerged as important tools for both treating and preventing HIV. These antibodies target conserved regions of the HIV envelope, making them effective against a wide range of viral strains. In clinical trials, bNAbs like 3BNC117 and 10-1074 have delayed viral rebound after ART interruption, particularly in individuals with antibody-sensitive reservoirs (Ismail et al., 2021). Combining multiple bNAbs can further enhance their efficacy and reduce the risk of viral escape.

Immune-based therapies, such as chimeric antigen receptor (CAR) T cells and natural killer (NK) cell engagers, are also being studied to enhance the immune system's ability to clear HIV-infected cells. For instance, CAR-T cells engineered to target HIV proteins have shown promise in preclinical models, though challenges related to persistence and exhaustion remain (Chou et al., 2024). Similarly, bispecific antibodies that engage NK cells to kill HIV-infected cells are being developed to augment the "kill" phase of shock-and-kill strategies.

5. Immune Modulation and Targeted Activation

Also, besides the primary cure strategies, research shows that scientists are looking into ways to adjust and activate the immune system to boost its capacity to wipe out or keep HIV in check. These methods aim to reverse latency, boost immune functions, and specifically target HIV-infected cells without causing widespread immune activation (Chou et al., 2024).

5.1 Toll-Like Receptor (TLR) Agonists

Toll-like receptors (TLRs) are key components of the innate immune system that recognize pathogen-associated molecular patterns and trigger immune responses. Scientists have studied TLR agonists, like GS-9620 (Vesatolimod), to see if they can wake up dormant HIV and beef up antiviral immunity (Ismail et al., 2021). TLR-7 and TLR-8 agonists, in particular, can stimulate dendritic cells and T cells, leading to the production of cytokines like interferons, which promote immune activation and latency reversal.

Several preclinical studies have revealed that TLR-7 agonists can induce low levels of HIV RNA expression in latently infected cells, making them potential candidates for the "shock" phase of shock-and-kill strategies (Chou et al., 2024). In a Phase Ib clinical trial, GS-9620 was well-tolerated and induced interferon-stimulated gene expression, suggesting its potential to enhance immune responses against HIV. However, the latency-reversing effects of TLR agonists have been modest compared to other LRAs, and their ability to reduce the reservoir size remains unclear. Pairing TLR agonists with other immune-boosting therapies, such as bNAbs or therapeutic vaccines, may improve their efficacy (Ismail et al., 2021).

5.2 HIV-Specific Antigens and Virus-Like Particles (VLPs)

HIV-specific antigens, such as virus-like particles (VLPs), are structured to mirror the structure of HIV without being infectious. These particles can stimulate immune responses and selectively reactivate latently infected cells that express HIV-specific T-cell receptors (Chou et al., 2024). VLPs have shown promise in preclinical studies, where they induced robust latency reversal in CD4+ T cells from individuals on ART. Unlike broad-acting LRAs, VLPs target only HIV-specific cells, minimizing off-target effects and reducing the risk of toxic immune activation.

One study demonstrated that VLPs derived from the quasi-species of HIV-infected patients outperformed other LRAs in reactivating latent HIV (Ismail et al., 2021). The level of latency reversal achieved by VLPs was comparable to that induced by strong T cell activators like PMA/ionomycin, but with greater specificity. This targeted approach could be beneficial for individuals treated during acute infection, where the reservoir is more skewed toward HIV-specific T cells. However, more studies are needed to determine the effectiveness of VLPs in individuals treated during chronic infection and to address potential subtype-specific differences in the VLP design.

5.3 Immune Checkpoint Blockade

Chronic HIV infection leads to immune exhaustion, characterized by the upregulation of immune checkpoint proteins like PD-1, CTLA-4, and TIM-3 on T cells. These proteins suppress T cell function, allowing HIV to persist despite ART. Immune checkpoint inhibitors (ICIs), such as anti-PD-1 and anti-CTLA-4 antibodies, have been researched on in terms of T cell exhaustion reversal and enhancing immune responses against HIV (Chou et al., 2024).

In preclinical studies, ICIs have shown the ability to reverse latency and improve HIV-specific T-cell function. For example, in SIV-infected macaques, CTLA-4 blockade reduced viral RNA levels in lymph nodes and enhanced SIV-specific CD4+ and CD8+ T cell responses (Ismail et al., 2021). In humans, anti-PD-1 therapy (e.g., pembrolizumab) has been tested in HIV-infected individuals with cancer. While some studies found a transient increase in HIV RNA levels and improved T cell function, others did not find a statistically significant reduction in the reservoir size. These conflicting findings highlight the complexity of immune checkpoint blockade in HIV cure strategies and the need for further optimization.

5.4 Combination Approaches

Combining immune modulation strategies with other cure approaches could enhance their effectiveness. For example, TLR agonists or VLPs could be used to reactivate latent HIV, while immune checkpoint blockade or bNAbs could enhance the clearance of reactivated cells (Chou et al., 2024). Likewise, therapeutic vaccines could ready the immune system to identify and destroy HIV-infected cells after latent phase is reversed. Combining HIV cure strategies could address the limitations of individual approaches for a more effective and lasting cure.

Conclusion

The persistence of latent HIV reservoirs remains the key barrier to a cure despite the success of antiretroviral therapy (ART) in controlling viral replication. This review highlights five key strategies: (1) shock-and-kill, which reactivates latent HIV for immune clearance; (2) block-and-lock, aiming to silence viral transcription permanently; (3) gene editing and stem cell transplantation, which offers precise removal or resistance to HIV; (4) broadly neutralizing antibodies (bNAbs) and immune-based therapies, enhancing immune responses; and (5) immune modulation, including TLR agonists and immune checkpoint blockade. Each strategy remains promising but faces challenges such as reservoir

heterogeneity, immune evasion, and scalability. Combining these approaches - such as pailatency-reversing agents with immune-boosting therapies - may offer the best path forward. Insights from Chou et al. (2024) and Ismail et al. (2021) emphasize the need for continued innovation and global accessibility in HIV cure research. While a cure remains elusive, the progress made provides hope that a combination of strategies could one day achieve durable viral control or eradication.

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