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A Phased HIV-Based Vector Therapy for Targeting Active and Latent Infection – A Theoratical Model for Eradication

Sankara Narayanan Ravi[1]

[1] 6th Year, 12Th Semester, Medicine, Tbilisi State Medical University.

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Abstract: Despite the success of antiretroviral therapy (ART), HIV remains incurable due to the persistence of latent viral reservoirs that evade immune clearance and therapy. Current strategies targeting latency, such as "shock-and-kill" and "block-and-lock," have shown limited success and safety concerns. We propose a novel phased gene therapy approach using engineered HIV-derived lentiviral vectors to target both actively replicating and latent HIV. In the first phase, a Therapeutic Interfering Particle (TIP) or antiviral gene cassette is delivered to suppress active HIV replication. In the second phase, following suppression, a latency-reversing or cytotoxic payload is introduced via a second vector to reactivate and eliminate reservoir cells. This staged model leverages the natural tropism and replication biology of HIV to deliver therapy precisely and sequentially. If validated, this strategy could offer a path toward a functional or sterilizing cure for HIV infection.

Keywords: *HIV Cure, Gene Therap , Vectors, Therapeutic Interfering Particles, Phased Treatment.*

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I. BACKGROUND AND RATIONALE

Lentiviral vectors based on deactivated HIV-1 have been widely used in gene therapy due to their efficiency in transducing both dividing and non-dividing cells and their capacity for long-term gene expression. These vectors are considered safe when properly engineered, and have been approved for therapeutic use in diseases such as SCID and β-thalassemia. In parallel, Therapeutic Interfering Particles (TIPs)—engineered defective viruses that require wild-type HIV to replicate—have shown promise in both modeling and animal studies, as they can outcompete the replicating virus and reduce viral loads [1].

Several recent studies have explored using CRISPR-Cas9 to excise integrated HIV DNA or target essential viral genes [2]. While promising, these techniques face challenges such as off-target effects, delivery limitations, and inability to target deeply latent cells. Separately, latency-reversing agents (LRAs) such as HDAC inhibitors have been studied to "shock" HIV out of latency, but success has been limited due to poor immune clearance and toxicity concerns [3].

Importantly, no current strategy effectively combines the sequential targeting of both active and latent HIV in a staged fashion using therapeutic vectors derived from the virus itself. Our hypothesis builds upon these efforts by proposing a multi-phased therapeutic intervention using modified HIV-based vectors to deliver payloads targeted to both viral states.

II. HYPOTHESIS

We hypothesize that a phased therapeutic approach using engineered HIV-derived vectors can sequentially eliminate both active HIV replication and latent HIV reservoirs. In this strategy:

Phase 1 involves the administration of an HIV-based vector carrying either a TIP, antiviral gene cassette, or CRISPR construct aimed at disrupting actively replicating virus. This vector can replicate only in the presence of wild-type HIV and suppresses its replication cycle.

Phase 2 involves delivering a latency-reversing agent or a suicide gene via another vector, timed to follow the initial suppression of active virus. This phase aims to activate and eliminate latently infected cells, potentially through cytotoxic or immune-directed mechanisms .

This biphasic model, if successful, may represent a viable path to a functional or sterilizing cure by combining the strengths of gene therapy, latency reversal, and viral interference in a single coordinated treatment protocol.

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III. PROPOSED METHOD AND CONCEPTUAL MODEL

➢ *Overview of the Two-Phase Strategy*

We propose a two-phase therapeutic model using HIV-derived lentiviral vectors:

- *Phase 1: Targeting Active HIV*

Use of a Therapeutic Interfering Particle (TIP) or CRISPR-based gene construct packaged in a replication-deficient HIV vector.

Upon administration, the TIPs replicate only in cells actively producing wild-type HIV, hijacking the replication machinery to produce non-infectious particles and thereby reducing viral load.

CRISPR constructs may be directed at conserved regions of the HIV genome (e.g., gag, pol, LTR) to excise or disable proviral DNA in actively infected cells.

- *Phase 2: Targeting Latent Reservoirs*

After suppression of active viremia, a second lentiviral vector is introduced.

➢ *This Vector May Deliver:*

A latency-reversing agent (LRA) gene (e.g., HDAC inhibitor, PKC agonist)

Or a suicide gene (e.g., inducible caspase-9) under a latency-specific promoter.

Upon reactivation of latent cells, these vectors express toxic or immune-activating products to eliminate the formerly dormant reservoir cells.

➢ *Hypothetical Preclinical Experiment*

Model: HIV-infected humanized mice (e.g., NSG mice reconstituted with human CD4+ T cells)

- *Groups:*

✓ Group 1: Standard ART control
✓ Group 2: TIP vector alone
✓ Group 3: TIP + latency-targeting vector (phased 2 weeks apart)

➢ *Outcomes Measured:*

- Plasma viral load (qRT-PCR)
- Proviral DNA in tissues (ddPCR)
- Reservoir size (Alu-PCR, viral outgrowth assays)
- CD4+ T-cell counts
- Inflammatory markers (IL-6, TNF-α)

This model would help demonstrate if the phased therapy reduces both active and latent infection more effectively than existing approaches.

IV. DISCUSSION

This hypothesis builds on existing gene therapy and latency reversal concepts but introduces a novel phased delivery paradigm to sequentially target active replication and latent reservoirs. The rationale lies in the fact that early intervention with TIPs or CRISPR could drastically reduce circulating virus and infected cell turnover, preparing the system for more effective latency-targeting therapy.By employing HIV-derived vectors, we utilize the virus's own tropism and integration efficiency to deliver payloads directly to HIV-susceptible cells. This could help bypass barriers seen in systemic LRA administration, such as off-target toxicity or inefficient tissue penetration.

➢ *There are Foreseeable Challenges:*

- Immune recognition of therapeutic vectors
- Precise timing of phase transitions
- Potential for insertional mutagenesis
- Ensuring the second vector only activates in reactivated cells

Nevertheless, this model provides a framework that could guide preclinical development and design of future clinical trials. If successful, it could advance the field toward a functional or sterilizing HIV cure.

V. CONCLUSIONS

The persistence of latent HIV reservoirs remains the key obstacle to achieving a cure , despite decades of progress in antiviral therapy. We propose a novel , staged therapeutic strategy that uses engineered HIV based vectors to first suppress active viral replication and then target latent reservoirs. This approach integrates concepts from therapeutic interfering particles (TIPs), gene editing , and latency reversal in phased , biologically logical sequence , leveraging the virus's own replication machinery for therapeutic benefit

While still hypothetical , this model offers a fresh perspective on how HIV biology can be turned against itself, potentially ivercoming the long standing barriers to cure. If validated in preclinical models,this phased vector system couldbecome a transformative framework in HIV CURE research, deserving of further investigation through laboratory experimentation and translational studies.

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