

Reverse Engineering of HIV Based on the Theory of Order Variation: 7 Vulnerable Steps and Integrated Therapeutic Strategies

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Abstract

Human Immunodeficiency Virus (HIV) is one of the most evolutionarily successful pathogens to date. Through three core mechanisms—latency, high mutation rate, and immune exhaustion—it continuously disrupts the immune order of the host, making a radical cure a global challenge. Based on the systematic scientific framework of the Theory of Order Variation, this paper conducts a full-chain reverse engineering dissection of the complete life cycle of HIV and for the first time establishes a **7-step vulnerable point order variation disruption model**, corresponding to seven key order variation links of the virus: adsorption, membrane fusion, uncoating, reverse transcription, integration and latency, transcription and replication, and assembly and budding. For each step, its structural vulnerabilities, functional dependencies and order stability defects are identified, and precise intervention strategies of targeted order disruption, controllable entropy increase, and forced exposure of closed order are proposed.

On this basis, this paper originally puts forward the integrated molecular concept of **"Coupling → Denaturation + Exposure"**: a single molecular platform simultaneously achieves three functions—viral targeted coupling, structural denaturation and inactivation, and forced exposure of latent closed order, breaking through the temporal dislocation and efficiency bottleneck of the traditional "stepwise kick-and-kill" model. Combining the global cutting-edge clinical evidence from 2025 to 2026 (bispecific TCR antibody IMC-M113V, $\gamma\delta$ T cell broad-spectrum killing, rapamycin for anti-immune exhaustion, etc.), a time-optimal three-stage integrated therapeutic system is constructed: order disruption and virus clearance (inhibition of active virus) → order pulling and exposure (activation of latent reservoir) → order elimination and eradication (clearance of activated infected cells).

This study for the first time deeply integrates the Theory of Order Variation with viral reverse engineering, providing a quantifiable, verifiable and transformable original theoretical system and experimental path for the functional cure of HIV.

Keywords: HIV; Theory of Order Variation; reverse engineering; latent activation; forced exposure of closed order; coupling molecule; functional cure

Subject Classification: Virology; Immunology; Systems Biology; Drug Design; Theoretical Medicine

1 Introduction

1.1 The Essence of HIV in the Theory of Order Variation: High-Entropy Invasion and Immune Order Collapse

HIV is not a simple pathogen, but a highly entropy-order variant that is highly adapted to the host order field and takes the destruction of the immune orthogonal structure as its survival basis. Its core survival strategies can be summarized into three types of order variation behaviors:

1. Latent closed order: After integrating into the genome, the virus enters a closed-order folded state with low expression and low immunogenicity, forming a latent reservoir that cannot be recognized by drugs and the immune system;
2. High-entropy mutation: The reverse transcriptase has no proofreading function and continuously produces sequence chaos to achieve order state escape;
3. Immune order exhaustion: Sustained antigen stimulation leads to the collapse of the CD4⁺ /CD8⁺ orthogonal balance and the complete failure of the immune surveillance order.

1.2 Order Variation Defects of the Existing Therapeutic System

Current Antiretroviral Therapy (ART), kick-and-kill strategies, gene editing and immunotherapy all have three major bottlenecks: incomplete order control, mismatched timing, and inaccurate targeting:

- Only inhibiting replication without destroying the latent closed order;
- Temporal dislocation between activation and clearance, which is likely to cause secondary viral spread;
- Lack of integrated molecular tools, making it difficult to synchronously achieve "capture—denaturation—exposure—killing".

1.3 The Subversive Value of the Theory of Order Variation

The Theory of Order Variation holds that:

Living system = stable order structure + orthogonal energy channel + controllable entropy flow

Virus = local order defect + high-entropy proliferation + host order hijacking

The essence of curing HIV is not simply inhibiting replication, but:

Reconstructing the host immune order + targeted destruction of the viral functional order + forced exposure of the latent closed order + controllable entropy increase to disintegrate the viral structure.

This paper for the first time applies the Theory of Order Variation to the reverse analysis of the entire HIV life cycle and establishes a quantifiable, intervenable and transformable therapeutic system.

2 Reverse Engineering of the 7-Step HIV Life Cycle and Vulnerable Point Localization

2.1 7-Step Order Variation Process and Vulnerability Rating

Step	Order Variation Behavior	Biological Process	Core Vulnerability	Vulnerability Rating
1	Capture: Order Anchoring	gp120 binding to CD4	Highly conserved conformation, non-escapeable	★★★★★
2	Entry: Order Fusion	gp41-mediated membrane fusion	Conformational changes strictly dependent on timing	★★★☆☆
3	Uncoating: Order Depolymerization	Capsid depolymerization	Dependent on host factors, weak stability	★★★☆☆
4	Transcription: Order Rewriting	RNA→DNA reverse transcription	No proofreading, high mutation and high entropy increase	★★★★☆

5	Hiding: Order Folding	Integration into genome and establishment of latency	Fragile closed-order state, easily forced to expose	★★★★★
6	Replication: Order Amplification	Viral transcription and translation	Fully dependent on host synthesis order	★★★★☆☆
7	Dissemination : Order Release	Protease cleavage + budding	Extremely high assembly precision requirement, prone to disorder	★★★★★

2.2 Order Variation Attack Strategy for Each Step

1. Capture: Block the gp120-CD4 order coupling to prevent viral anchoring;
2. Entry: Interfere with the gp41 conformational order to block membrane fusion;
3. Uncoating: Destroy capsid stability to prevent order depolymerization;
4. Transcription: Induce reverse transcription errors and disintegrate via entropy increase overload;
5. Hiding: Force the exposure of closed order to break latency;
6. Replication: Interfere with the transcription and translation order to block amplification;
7. Dissemination: Inhibit protease cleavage to produce non-infectious virions during assembly.

3 Core Framework of the Theory of Order Variation: The Order State Essence of HIV

3.1 Theory of Order Variation - HIV Corresponding System

Concept of the Theory of Order Variation	HIV Biological Corresponding	Therapeutic Significance
Closed order state	Latent reservoir: gene	Need to pull order,

	silencing, low expression	expose and break folding
Open order state	Active replication: high expression, high immunogenicity	Can be cleared by the immune system and drugs
Orthogonal structure	gp120 conserved binding domain, CD4 orthogonal interface	Target conserved order to prevent escape
Order energy	Replication efficiency, conformational stability	Reduce order energy → viral inactivation
Controllable entropy increase	Induce mutation overload and conformational disorder	Targeted disintegration of virus without damaging the host
Order coupling	Molecular binding, protein-protein interaction	Foundation for coupling molecule design

3.2 Kinetics of Closed Order → Open Order Conversion

Latent activation is essentially the unwinding of folded order, opening of silent order and restart of transcription order.

There is a clear time window for activation kinetics:

- 0–24h: Loosening of closed order
- 3–5 days: Peak of viral protein expression (optimal killing window)
- After 7 days: Increased risk of secondary latency

Timing optimization is the core of successful cure.

4 Theory of Order Variation-Integrated Therapy: A Time-Optimal Three-Stage Regimen

4.1 Step 1: Order Disruption – Suppression of Active Virus (1–2 weeks)

Objective: Reduce the systemic viral order load and stabilize the host immune order

Strategy: ART + bispecific antibody IMC-M113V

Mechanism: Block the adsorption order, clear free virus, and reduce the infection pool

4.2 Step 2: Order Pulling – Activation of Latent Closed Order (3–5 days)

Objective: Force the exposure of folded order and fully reveal latent virus

Strategy: HDACi/PKC modulator (SUW133) + low-intensity order field intervention

Key: Precisely capture the expression peak window

4.3 Step 3: Order Elimination – Clearance of Activated Infected Cells

Objective: Completely clear infected cells during the open order peak period

Strategy: CAR-T / $\gamma\delta$ T + rapamycin (anti-exhaustion)

Mechanism: Immune order reconstruction + targeted killing + extension of effector window

4.4 Core Order Variation Hypotheses (Directly Experimentally Verifiable)

1. The 3rd to 5th day after activation is the open order peak of the virus, with the highest clearance efficiency;
2. Rapamycin can stabilize the immune order, prevent exhaustion and expand the clearance window;
3. $\gamma\delta$ T cells are not restricted by MHC and have stronger killing effect on open-order HIV-infected cells;
4. Temporal dislocation will lead to secondary latency and order reconstruction rebound.

5 Original Core: Coupling → Denaturation + Exposure Integrated Molecule

5.1 Order Variation Defects of Traditional Strategies

- Stepwise administration: Separation of activation, clearance and coupling;
- Temporal dislocation: Early activation and late killing;
- Lack of integrated tools: Inability to synchronously capture, denature and expose.

5.2 Design of Coupling Molecule Based on the Theory of Order Variation (Original)

A single molecule with three orthogonal functional domains:

1. Coupling domain: Target the gp120 conserved order to precisely capture the virus;
2. Denaturation domain: Force the distortion of conformational order and disintegrate via entropy increase;
3. Exposure domain: Penetrate cells and expose the latent closed order.

Single administration = virus capture + denaturation and inactivation + latent exposure + immune clearance

5.3 Technical Feasibility

- Mature bispecific antibody platform;
- CD4-mimetic peptides can achieve conformational destruction;
- LRA small molecules can be conjugated to achieve latent activation;
- Fully engineerable and clinically transformable.

6 Testable Scientific Hypotheses (Core Innovations of the Paper)

1. Time-optimality hypothesis: The 3rd to 5th day after latent activation is the open order peak, with the highest clearance efficiency at this time;
2. Coupling molecule hypothesis: Integrated molecules can synchronously achieve coupling, denaturation and exposure with higher efficiency than stepwise strategies;
3. $\gamma\delta$ T broad-spectrum hypothesis: $\gamma\delta$ T cells exert potent MHC-independent killing on open-order HIV-infected cells;
4. Rapamycin order stabilization hypothesis: Rapamycin stabilizes the immune orthogonal order and improves the persistent clearance capacity;
5. Controllable entropy increase hypothesis: Targeted induction of viral entropy increase overload can achieve structural disintegration without damaging the host.

7 Discussion

7.1 Original Contributions of This Study

1. For the first time, a complete system of the Theory of Order Variation-HIV reverse engineering is established;
2. For the first time, a 7-step vulnerable point order variation model is proposed;
3. For the first time, the core status of closed order/open order in HIV cure is defined;
4. The original integrated molecular concept of Coupling \rightarrow Denaturation + Exposure is put forward;

5. A time-optimal three-stage integrated therapeutic regimen is constructed.

7.2 Connection with International Cutting-Edge Research

- Docking with the clinical data of the bispecific TCR antibody IMC-M113V;
- Docking with the latest research on $\gamma\delta$ T cells, CAR-T and rapamycin for anti-immune exhaustion;
- Docking with the clinical progress of latent activators such as SUW133;
- Can be directly transformed into experimental protocols and clinical trial designs.

7.3 Limitations and Future Directions

- Need for in vitro/animal experiments to verify the time window;
- Need for specific structural design and synthesis of coupling molecules;
- Expandable to a combined system of orthogonal magnetic field, order field intervention and traditional Chinese medicine order regulation.

8 Conclusion

Based on the systematic framework of the Theory of Order Variation, this paper completes the reverse engineering analysis of the entire HIV life cycle, establishes a 7-step vulnerable point order disruption system, and reveals the core status of latent closed order, open order peak, orthogonal structure and controllable entropy increase in HIV cure. Two original strategies are proposed: a time-optimal three-stage integrated therapy and a Coupling \rightarrow Denaturation + Exposure integrated molecule, providing a brand-new theory, verifiable hypotheses and transformable paths for the functional cure of HIV.

The Theory of Order Variation provides a holistic, systematic and structural new paradigm beyond traditional virology for cracking AIDS.

Conflict of Interest

The author declares no conflict of interest.

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Statement of Originality

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