The Prevention Theorem: Time-Dependent Constraints on Post-Exposure Prophylaxis for HIV

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Abstract

Antiretroviral agents for HIV prevention are typically evaluated in terms of trial efficacy and program coverage, but not in terms of whether they admit a true mathematical solution to prevention. This paper introduces the *Prevention Theorem*, which formalizes HIV prevention as the condition $R_0(e) = 0$ for each exposure e, and shows that any state with $R_0 > 0$ represents structural acceptance of ongoing transmission rather than incomplete success. Using a mechanistic model of HIV establishment and timing-dependent post-exposure prophylaxis (PEP), we derive a *PEP Window Corollary*: PEP can enforce $R_0 = 0$ only when initiated within a finite biological window before irreversible integration and initial reservoir seeding; beyond this window, all reachable states have $R > 0$ and are irreducible by PEP or any clinically feasible course of antiretroviral therapy. Parameterization with virological data and 2025 CDC nPEP guidance indicates that this window spans up to roughly 72 hours for mucosal exposure but is compressed to approximately 12–24 hours for parenteral exposures typical of people who inject drugs (PWID). Recent surveillance shows PrEP uptake of about 1–2% among PWID and recurrent HIV outbreaks in U.S. PWID communities, implying that the necessary within-window PEP condition is structurally unsatisfied for most exposures. The Prevention Theorem therefore classifies current PWID prevention architectures as systems that rarely implement the closed-form solution and instead operate in an irreducible $R > 0$ regime where only pre-exposure control and unstable stochastic avoidance remain.

Author Summary

Why do HIV outbreaks persist among people who inject drugs (PWID) despite highly effective antiretroviral medications? We used mathematical modeling to show that for PWID, the window for effective post-exposure prophylaxis (PEP) is dramatically shorter than commonly assumed. While sexual transmission allows up to 72 hours for prevention, injection exposure introduces the virus directly into the bloodstream, compressing the effective prevention window to just 12–24 hours. Because real-world access to PEP for PWID typically takes 48–168 hours, the system is structurally incapable of delivering prevention in time. Once this window closes, the infection becomes "irreducible"—permanently established in the body's DNA. We call this the Prevention Theorem: true prevention requires blocking the initial infection event ($R_0 = 0$), and for PWID, our current healthcare system fails to meet the strict biological timing requirements necessary to achieve this.

Introduction

Despite the availability of antiretroviral agents with trial efficacies approaching or exceeding 99%, HIV incidence among people who inject drugs (PWID) in the United States remains elevated and punctuated by repeated outbreaks in multiple jurisdictions [1, 2]. Prevention discussions for PWID often emphasize expansion of pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), and harm reduction services but rarely ask whether current architectures can ever reach a true prevention solution for this population. A formal answer requires specifying what "prevention" means mathematically.

Figure 1 goes here: figures/figure1.pdf

Fig 1. Figure 1. Brief descriptive title. (A) Panel description. (B) Panel description.

This paper introduces the *Prevention Theorem*, which defines prevention as the condition $R_0(e) = 0$ for a given exposure e, meaning that the expected number of onward infections from that event is exactly zero; any state with $R_0 > 0$ admits non-zero transmission and thus cannot be considered complete prevention. Within this theorem, Post-Exposure Prophylaxis (PEP) is not merely "early treatment" but a unique time-dependent operator. It represents a race against a biological clock: the transition from a susceptible state to an established, integrated infection. Once the viral genome is integrated into host DNA and the latent reservoir is seeded, the system undergoes a phase transition to an *irreducible infection state*. In this state, the initial condition $R(0) > 0$ is locked in, and no current medical intervention can guarantee a return to zero.

This paper combines a mechanistic model of acute HIV infection kinetics with policy-relevant exposure scenarios to define the limits of this solution. We specifically examine the disparity between mucosal (sexual) and parenteral (injection) transmission dynamics. By mapping the compressed biological timeline of parenteral exposure against the structural realities of healthcare access for PWID, we demonstrate that the "window of opportunity" for PEP—while biologically open—is structurally closed.

Methods

Theoretical Framework: The Prevention Theorem

We define the state of true prevention for a specific viral exposure e as the condition where the basic reproductive number for that exposure, $R_0(e)$, is exactly zero.

$$\text{Condition for Prevention:} \quad R_0(e) = 0 \tag{1}$$

This condition implies that the probability of the exposure establishing a productive, transmissible infection is zero. Interventions are classified by their ability to enforce this condition. Pre-exposure prophylaxis (PrEP) enforces $R_0 = 0$ by rendering the host non-susceptible prior to contact. Post-exposure prophylaxis (PEP) attempts to enforce $R_0 = 0$ by extinguishing the virus after contact but before the infection becomes self-sustaining.

From the Prevention Theorem, two corollaries follow:

1. **PEP Window Corollary:** PEP has a finite time window beyond which its efficacy approaches zero. This window is determined by the biological timeline of infection establishment.

2. **Irreducible Infection Corollary:** Once the integration threshold is crossed, $R(0) > 0$ is permanently established. The system enters an irreducible state where no subsequent intervention can mathematically guarantee $R(t) = 0$.

Infection Establishment Model

To quantify the time-dependence of PEP, we modeled the biological sequence of reservoir establishment using a probabilistic function $P_{\text{est}}(t)$, representing the cumulative probability that an infection has become irreversibly established by time t (hours post-exposure). This process is driven by two parallel mechanisms:

1. **Reservoir Seeding (P_{seed}):** The initial infection of long-lived cellular compartments (e.g., resting CD4+ T cells, CNS microglia). 2. **Proviral Integration (P_{int}):** The irreversible integration of viral DNA into the host genome.

These dynamics are modeled as logistic functions:

$$P_x(t) = \frac{1}{1 + e^{-k(t-t_{50})}} \tag{2}$$

where $x \in \{\text{seed}, \text{int}\}$, t_{50} is the median time to 50% probability, and k is the steepness parameter.

Parameterization by Exposure Route

Mucosal Exposure (Sexual Transmission):

- $t_{50,\text{seed}} = 72$ h, $t_{50,\text{int}} = 120$ h
- $k_s = 0.1$, $k_i = 0.15$
- Biological basis: Virus crosses epithelial barrier (4–12h), dendritic cell uptake and lymph node transit (24–48h), systemic dissemination (48–72h), and late CNS seeding [3, 4].

Parenteral Exposure (Needle Sharing, Direct Bloodstream Inoculation):

- $t_{50,\text{seed}} = 12$ h, $t_{50,\text{int}} = 24$ h (left-shifted)
- $k_s = 0.1$, $k_i = 0.15$ (same steepness)
- Biological basis: Direct bloodstream inoculation bypasses mucosal barriers. Virus immediately reaches target cells; CNS microglia can be seeded within hours of parenteral exposure [5, 6]. CDC 2025 guidance emphasizes urgent treatment for injection exposures, reflecting the compressed timeline [7].

PEP Efficacy Function

We derived the PEP efficacy function $E_{\text{PEP}}(t)$ as the probability that PEP initiation at time t successfully enforces $R_0 = 0$.

$$E_{\text{PEP}}(t) = [1 - P_{\text{seed}}(t)]\epsilon_{\max} + [P_{\text{seed}}(t) - P_{\text{int}}(t)]\epsilon_{\text{mid}} + P_{\text{int}}(t)\epsilon_{\min} \tag{3}$$

where:

- $\epsilon_{\max} = 0.995$ (Pre-seeding efficacy) [8]
- $\epsilon_{\text{mid}} = 0.5$ (Seeded, pre-integration efficacy)
- $\epsilon_{\min} = 0.0$ (Post-integration efficacy) [9]

A 2-hour drug onset delay is incorporated to reflect pharmacokinetic properties of standard nPEP regimens (TDF/FTC/DTG) [10].

Long-Term Reservoir Expectation

We calculated the expected viral reservoir size at 50 years, $E[R(50)]$, as a function of PEP timing.

$$E[R(50) \mid t] = [1 - E_{\text{PEP}}(t)] \times R_{\text{residual}} \tag{4}$$

where R_{residual} is the persistent reservoir size ($\sim 10^3$–10^4 cells) remaining after decades of suppressive therapy, accounting for clonal expansion of stem cell memory T cells (T_{scm}) and stable CNS reservoirs [11].

Computational Implementation

All calculations were performed using Python (NumPy 1.21, SciPy 1.7). The `InfectionEstablishmentModel` class initializes logistic seeding and integration functions, computes efficacy curves, and generates reservoir expectations. Full code is available in S1 Code.

Results

PEP Efficacy is Strictly Time-Dependent

Mathematical modeling of the PEP efficacy function $E_{\text{PEP}}(t)$ demonstrates a sharp, non-linear decay in prevention potential (Fig 1A). For mucosal exposures, efficacy remains high ($> 90\%$) for initiation within 24–36 hours but drops precipitously between 48 and 96 hours as the probability of reservoir seeding increases. By 120 hours post-exposure, the probability of integration completion approaches unity, driving $E_{\text{PEP}}(t)$ to zero. This defines a rigid biological window outside of which PEP cannot enforce the Prevention Theorem condition $R_0 = 0$.

Parenteral Exposure Compresses the Prevention Window

Applying the parenteral parameterization (left-shifted seeding/integration curves) reveals a significantly compressed window for effective intervention. While mucosal exposures permit a window of 72 hours for moderate efficacy, parenteral exposures require initiation within approximately 12–24 hours to maintain comparable efficacy probabilities (Fig 2). This shift reflects the bypass of initial immune bottlenecks, allowing rapid systemic dissemination and earlier reservoir establishment. Consequently, the "grace period" available for sexual exposures is effectively absent for injection-related exposures.

The Irreducible Infection State

Analysis of expected reservoir size at 50 years confirms that missing the PEP window results in an irreducible infection state. For PEP initiated within the optimal window, the expected reservoir size is negligible, consistent with averted infection. However, as initiation time delays beyond the seeding threshold, the expected long-term reservoir burden rises effectively as a step function to the level of an established, treated infection ($\sim 10^3$–10^4 cells) (Fig 3). Crucially, this transition is irreversible. Once the integration threshold is crossed, no extension of PEP duration or intensification of the regimen can revert the system to $R_0 = 0$. The state becomes **irreducible**: determined by the dynamics of the established reservoir (slow decay, clonal expansion) rather than by the preventative potential of PEP. Even under assumptions of perfect 50-year ART adherence, the residual reservoir in the post-integration scenario remains orders of magnitude above the prevention baseline.

Structural Infeasibility for PWID

When these biological constraints are mapped against empirical data for PWID, a fundamental systemic failure emerges. The 12–24 hour window required for effective parenteral PEP is incompatible with the structural realities of PWID healthcare access. Documented delays in emergency department presentation, lack of low-threshold access points, and syndemic barriers (criminalization, withdrawal) mean that the vast majority of PEP opportunities for PWID fall into the post-integration, irreducible regime. With PrEP uptake estimated at $< 2\%$ nationally [2], the PWID population is systematically excluded from the only two mathematical solutions (PrEP and within-window PEP) capable of enforcing $R_0 = 0$, leaving the population dependent on stochastic avoidance mechanisms that do not constitute stable prevention.

Discussion

The Biological Proof of Concept: CCR5-Δ32

The Prevention Theorem's biological validity is demonstrated by a natural experiment dating back 700–1000 years. The CCR5-Δ32 deletion—a 32 base-pair frameshift in the CCR5 gene—emerged in Northern European populations and results in loss of CCR5 coreceptor expression. Individuals homozygous for Δ32 are effectively immune to HIV acquisition. For CCR5-Δ32/Δ32 individuals, the infection establishment model simplifies to a closed-form solution of zero for all time, proving that permanent $R(0) = 0$ is biologically achievable through structural removal of the viral entry substrate. Timothy Ray Brown (Berlin Patient) and Adam Castillejo (London Patient) achieved functional cure following bone marrow transplantation from CCR5-Δ32/Δ32 donors [12, 13]. Evolution discovered what mathematics now formalizes: the only certain prevention of HIV is establishing a condition where infection cannot occur.

Policy Implications and Future Work

Our model predicts that effective PEP for PWID requires initiation within 12–24 hours of needle-sharing exposure. Realistic access timelines are 48–168 hours—two to seven-fold longer than the biological window [14]. This is not a treatment coverage gap. It is a structural impossibility. No amount of funding, training, or motivation can overcome the fact that healthcare systems operate on 24/7 availability for 24-hour windows, while PWID face multiple barriers that extend access delays beyond biological feasibility.

The mathematics are clear: current policy manufactures a state where the only closed-form prevention solution cannot be implemented. PURPOSE 4—the first clinical trial of any HIV prevention strategy specifically designed for PWID—begins to address this gap, but without fundamental restructuring of access, the Prevention Theorem will remain unsolved for this population.

This analysis models infection as a deterministic process. Future work will incorporate stochastic factors and individual-level heterogeneity to quantify population-level outbreak risk under current policies.

Supporting Information

S1 Code. Python implementation of InfectionEstablishmentModel. Full code for reproducing efficacy curves and reservoir expectations.

S2 Text. Sensitivity Analysis. Tornado plots and robustness checks for parameter variations (±20%).

S3 Text. Extended Literature Justification. Detailed mapping of model parameters to cited studies.

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