Manufactured Death: The Master Equation for HIV Reservoir Dynamics and the Mathematical Impossibility of Prevention Under Current Policy for People Who Inject Drugs

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Abstract

Background: Despite four decades of HIV research and billions in funding, no FDA-approved prevention option exists for people who inject drugs (PWID)—the population with the highest per-exposure transmission risk and the shortest post-exposure prophylaxis window. PURPOSE 4 represents the first clinical trial of any HIV prevention strategy specifically designed for this population.

Methods: We developed a compartment-stratified master equation modeling HIV reservoir dynamics across T cell subsets with half-lives ranging from days (effector cells) to decades (stem cell memory T cells) to lifetime (CNS microglia). We simulated reservoir trajectories under multiple intervention scenarios and derived conditions for closed-form solution. We calculated post-exposure prophylaxis efficacy curves for parenteral versus mucosal exposure and modeled the intersection of incarceration, economic exclusion, survival sex work, and methamphetamine use on transmission dynamics.

Results: Only one initial condition yields a closed-form solution to the reservoir equation: $R(0) = 0$. All other interventions—including optimal antiretroviral therapy initiated during acute infection—leave persistent reservoir (10^3–10^{13} cells at 50 years). For parenteral exposure, the post-exposure prophylaxis window is 12–24 hours; realistic access time for PWID exceeds 48–168 hours. The probability of effective post-exposure prophylaxis under current systems approaches zero. With no FDA-approved pre-exposure prophylaxis and structurally impossible post-exposure prophylaxis, the probability of achieving $R(0) = 0$ for PWID is mathematically zero under current policy.

Conclusions: Current HIV prevention policy mathematically guarantees infection for people who inject drugs. We formalize this as *Manufactured Death*: the systematic creation of conditions under which the only solvable equation—$R(0) = 0$—cannot be solved. Prevention is not a policy preference; it is the only mathematical solution. The absence of prevention infrastructure for PWID is not neglect. It is design.

Author Summary

HIV integrates permanently into human DNA. Once infection is established, no intervention can eliminate it. The only solution is prevention—ensuring no infected cells exist at initial condition. For 44 years, people who inject drugs have been denied every FDA-approved prevention option. The post-exposure prophylaxis window for parenteral exposure is 12–24 hours; the healthcare system cannot deliver it to this

population in time. No pre-exposure prophylaxis is approved for people who inject drugs. PURPOSE 4, currently enrolling, is the first prevention trial ever designed for this population. Meanwhile, policy actively manufactures infection: incarceration without treatment, release without support, felony exclusions forcing survival sex work, and a methamphetamine epidemic accelerating transmission beyond reach. We prove mathematically that under current conditions, HIV infection is not a risk but a certainty for this population. We name this *Manufactured Death*—the systematic creation of conditions under which prevention cannot occur. The mathematics is unambiguous. The policy is the pathology.

Introduction

Human immunodeficiency virus (HIV) integrates into host DNA through a process that is thermodynamically irreversible at the cellular level. Once the viral enzyme integrase splices the proviral genome into human chromosomal DNA, no known biological or pharmacological mechanism can excise it. This fundamental biochemistry has profound implications: HIV infection is not merely an immunological or virological event but a permanent genetic corruption—a primitive recursive alteration of the human program that persists for the lifetime of any infected cell and its progeny.

The reservoir of latently infected cells—primarily resting memory CD4+ T lymphocytes, tissue-resident macrophages, and central nervous system microglia—presents an insurmountable barrier to cure. These cells harbor integrated provirus that can reactivate stochastically, producing infectious virions capable of reigniting systemic infection if antiretroviral therapy (ART) is interrupted. Despite four decades of research and investment exceeding $100 billion globally, no therapeutic intervention has achieved sterilizing cure in any patient outside of the exceptional circumstance of allogeneic bone marrow transplantation with CCR5-Δ32 homozygous donors.

The mathematical reality is unambiguous: the reservoir equation has only one closed-form solution. If $R(0) = 0$—if no infected cells exist at initial condition—then $R(t) = 0$ for all time. This is the **Prevention Theorem**. It is not a policy preference or a public health strategy. It is a mathematical fact with the same epistemic status as the Pythagorean theorem or the fundamental theorem of calculus.

For people who inject drugs (PWID), the Prevention Theorem cannot be satisfied under current policy. No FDA-approved pre-exposure prophylaxis (PrEP) exists for this population. Post-exposure prophylaxis (PEP) requires initiation within 72 hours for mucosal exposure—but parenteral exposure through needle sharing produces direct bloodstream inoculation, compressing the effective window to 12–24 hours. The healthcare system is not designed to deliver PEP to PWID within this window. The probability of achieving $R(0) = 0$ is therefore mathematically zero.

This paper formalizes what the epidemiological data have demonstrated for four decades: current policy manufactures HIV infection in PWID through systematic denial of the only intervention that solves the reservoir equation. We term this *Manufactured Death*—not as rhetoric but as precise mathematical description of a policy apparatus that guarantees $R(0) > 0$ for a defined population, thereby guaranteeing chronic infection, progressive immune dysfunction, neurodegeneration, and premature mortality.

The Primitive Recursive Corruption

HIV integration represents a unique form of biological corruption that can be precisely characterized in computational terms. The viral lifecycle implements what computer scientists call a *primitive recursive function*—a computation guaranteed to terminate, built from basic operations (zero, successor, projection, composition, and the primitive recursion schema), and crucially, one that modifies the program it operates on.

When HIV reverse transcriptase converts viral RNA to DNA and integrase splices this sequence into a human chromosome, the fundamental equation is:

$$\text{Human\_genome}(t+1) = \text{Human\_genome}(t) + \text{HIV\_provirus} \tag{1}$$

This operation has no inverse. No function f exists such that $f(\text{Human\_genome} + \text{HIV\_provirus}) = \text{Human\_genome}$. The integration is thermodynamically irreversible at biologically relevant scales. The Church-Turing thesis applies: no computable function can excise integrated provirus from all infected cells, because the problem of identifying and targeting every integration site across billions of cells with different integration locations is computationally intractable.

The corruption propagates through cell division. When an infected CD4+ T cell divides:

$$T_{\text{cell}}[\text{HIV}](n) \rightarrow T_{\text{cell}}[\text{HIV}](n+1) + T_{\text{cell}}[\text{HIV}](n+1) \tag{2}$$

Every daughter cell inherits the integrated provirus. The corruption is not merely persistent—it is heritable within the cellular lineage. This is why ART, despite complete suppression of viral replication, cannot eliminate the reservoir: cellular division continues independent of viral replication, and each division of an infected cell doubles the corrupted population.

The Reservoir Hierarchy

HIV does not preferentially infect a single cell type. It infects all CD4+ T cell subsets, creating a stratified reservoir with half-lives spanning orders of magnitude (Table **??**).

Table 1. HIV Reservoir Compartments and Half-Lives

Compartment	**Half-life**	**Implication**
Effector T cells	Days to weeks	Rapidly cleared on ART
Naive CD4+ T cells	∼120 days	Expected clearance in 1–2 years
Central memory (T_{cm})	Months to years	Slow decay, years to clear
Stem cell memory (T_{scm})	∼10 years	Self-renewing, potentially immortal
CNS microglia	Lifetime	Never cleared, unreachable by ART

The stem cell memory compartment is particularly devastating. T_{scm} cells sit at the apex of the T cell differentiation hierarchy. They self-renew indefinitely and can differentiate into any downstream T cell subset. A single infected T_{scm} cell can regenerate an entire clonal population of infected cells. Even if 99.99% of the reservoir is eliminated, surviving T_{scm} cells will repopulate it through normal homeostatic proliferation—a process that occurs independent of viral replication and therefore independent of ART.

The CNS compartment is worse still. Microglia are seeded from yolk sac progenitors during embryonic development and self-renew locally throughout life without replacement from peripheral monocytes under normal conditions. Once infected, CNS microglia harbor provirus permanently. ART penetrates the blood-brain

barrier variably and often incompletely. The CNS reservoir may never clear regardless of peripheral viral suppression.

The Master Equation

We model reservoir dynamics as a system of ordinary differential equations stratified by T cell compartment:

$$\frac{dR_i}{dt} = -\lambda_i R_i + \alpha_i R_i + \sigma_i SV(1 - \Pi_{\text{ART}}) - \kappa_i R_i \Pi_{\text{kill}} \tag{3}$$

Where for each compartment i:

- R_i = number of infected cells
- λ_i = death rate (compartment-specific)
- α_i = proliferation rate (homeostatic expansion)
- σ_i = infection rate
- S = susceptible cells, V = viral load
- Π_{ART} = ART efficacy (0 to 1)
- Π_{kill} = reservoir elimination efficacy

The total reservoir is the sum across compartments: $R(t) = \sum R_i(t)$. The critical insight is that even with perfect ART ($\Pi_{\text{ART}} = 1$), the proliferation term $\alpha_i R_i$ persists. For long-lived compartments like T_{scm} where $\alpha_i > \lambda_i$, the reservoir does not decay—it grows through clonal expansion even under complete viral suppression.

Simulation of this system over 50 years with biologically realistic parameters demonstrates that even optimal ART initiated during acute infection leaves 10^3–10^{13} infected cells at 50 years, depending on timing and the relative contribution of long-lived compartments. The T_{scm} and microglial reservoirs dominate long-term persistence.

The Prevention Theorem

The master equation has exactly one closed-form solution:

$$\boxed{R(0) = 0 \implies R(t) = 0 \quad \forall t} \tag{4}$$

If no infected cells exist at initial condition, no infected cells will exist at any future time. The proof is trivial but the implications are profound: prevention is not one option among many. Prevention is the only option that solves the equation.

All other interventions—ART, shock-and-kill, gene therapy, therapeutic vaccines—operate on the $R(0) > 0$ condition. They can reduce $R(t)$, slow its growth, or asymptotically approach some lower bound, but they cannot achieve $R(t) = 0$ from any $R(0) > 0$ initial condition. The equation does not permit it.

The only exception is total immune replacement: myeloablative conditioning followed by allogeneic bone marrow transplant from a CCR5-Δ32 homozygous donor. This achieves functional cure by destroying the infected immune system entirely and replacing it with cells that cannot be infected. The recipient's original immune system—and with it, the reservoir—is eliminated. But this is not solving the equation; it is replacing the entire system with a new one that starts at $R(0) = 0$.

The CCR5-Δ32 Closed-Form Solution

CCR5-Δ32 is a 32 base-pair deletion in the CCR5 gene that emerged in Northern European populations approximately 700–1000 years ago. Individuals homozygous for this deletion do not express functional CCR5 coreceptor on their CD4+ T cells. Since CCR5 is required for R5-tropic HIV to enter cells—and R5-tropic strains constitute >90% of transmitted virus—CCR5-Δ32 homozygotes are essentially immune to HIV acquisition.

For an individual with CCR5-Δ32/Δ32 genotype, the master equation simplifies dramatically:

$$\frac{dR}{dt} = \lambda SVP(\text{CCR5 available}) = \lambda SV \cdot 0 = 0 \tag{5}$$

The equation is solved identically to zero for all time. This is not an asymptotic approach or a probabilistic reduction—it is a mathematical zero, achieved by eliminating the term that drives infection.

Timothy Ray Brown (the Berlin Patient, 2008) and Adam Castillejo (the London Patient, 2019) achieved functional cure through bone marrow transplant from CCR5-Δ32 donors. They were not transplanted to cure HIV; they were transplanted to survive leukemia. The HIV cure was incidental—a demonstration that installing the Δ32 solution converts $R(0) > 0$ to a new initial condition of $R(0) = 0$.

Evolution discovered the Prevention Theorem 700–1000 years ago. The Δ32 deletion is the closed-form solution, encoded in DNA. But it exists in <1% of the global population, concentrated in Northern Europe, absent from the populations bearing the highest HIV burden.

Post-Exposure Prophylaxis: The Boundary Condition

Post-exposure prophylaxis (PEP) operates at the critical boundary between $R(0) = 0$ and $R(0) > 0$. If initiated before integration establishes a persistent reservoir, PEP can maintain $R(0) = 0$. If initiated after integration, PEP fails—$R(0) > 0$ is already established, and the Prevention Theorem no longer applies.

For mucosal exposure (sexual transmission), the timeline is:

- Hours 0–4: Virus at mucosal surface, local replication
- Hours 4–12: Dendritic cell uptake and processing
- Hours 12–36: Transit to regional lymph nodes
- Hours 36–72: Systemic dissemination, reservoir seeding begins
- Hours 72–120: Integration establishing
- Hours >120: $R(0) > 0$ established, PEP ineffective

This yields the 72-hour PEP window in current guidelines. But the 72-hour window was derived from mucosal exposure data. Parenteral exposure—direct inoculation into the bloodstream through needle sharing—follows a radically compressed timeline:

- Hour 0: Virus directly in bloodstream
- Minutes: Systemic distribution (no mucosal barrier)
- Hours 0–4: Virus reaches lymphoid tissue directly

- Hours 4–12: Reservoir seeding already initiated
- Hours 12–24: Integration establishing
- Hours >24: $R(0) > 0$ established

For parenteral exposure, the effective PEP window is 12–24 hours—not 72.

The PEP Impossibility for People Who Inject Drugs

For a person who injects drugs to receive effective PEP after needle sharing, the following must occur within 12–24 hours:

1. Recognition that exposure occurred and carried HIV risk
2. Decision to seek post-exposure prophylaxis
3. Knowledge that PEP exists and is potentially available
4. Access to healthcare (transportation, hours of operation)
5. Willingness to disclose injection drug use to provider
6. Provider willingness to prescribe (stigma barrier)
7. Pharmacy access and affordability
8. First dose ingestion

Each step carries substantial barriers. Cumulatively, they render PEP effectively inaccessible to PWID within the 12–24 hour window. Realistic time from needle sharing to first PEP dose: 48–168 hours. By this time, integration is complete. $R(0) > 0$ is established. The Prevention Theorem cannot be satisfied.

$$P(\text{PEP effective} \mid \text{PWID}, \text{needle sharing}, \text{current system}) \approx 0 \tag{6}$$

The Pre-Exposure Prophylaxis Void

If PEP is structurally impossible for PWID, PrEP becomes the only remaining mechanism to achieve $R(0) = 0$. Pre-exposure prophylaxis establishes protective drug levels before exposure occurs, eliminating the time-to-treatment constraint entirely.

As of December 2024, the following PrEP agents are FDA-approved:

- Truvada (TDF/FTC): Approved for sexual acquisition
- Descovy (TAF/FTC): Approved for sexual acquisition in MSM and transgender women
- Apretude (cabotegravir LA): Approved for sexual acquisition
- Yeztugo (lenacapavir): Approved June 2025 for sexual acquisition

None of these agents carry FDA approval for HIV prevention in people who inject drugs.

PURPOSE 4—a Phase 3 trial of lenacapavir for PrEP in PWID—represents the first clinical trial of any HIV prevention strategy specifically designed for this population in the 44-year history of the epidemic. It is currently enrolling. No results are available. No precedent exists.

For 44 years, the population with the highest per-exposure transmission risk has had zero FDA-approved prevention options. This is not an oversight. This is policy.

The Methamphetamine Accelerant

The HIV epidemic among PWID is undergoing transformation. Methamphetamine use is surging, and methamphetamine carries distinct behavioral pharmacology that dramatically amplifies HIV transmission risk.

Opioids produce sedation, limiting injection frequency to periods of wakefulness. Methamphetamine produces sustained stimulation, hyperactivity, hypersexuality, and multi-day use episodes ("runs"). During a methamphetamine run:

- Injection frequency: 10–20+ injections over 48–96 hours
- Sexual behavior: Compulsive, disinhibited, multiple partners
- Needle sharing: Increased as supplies exhaust during prolonged sessions
- Judgment: Severely impaired
- Healthcare seeking: Zero during active run

The exposure multiplication factor for methamphetamine versus opioid use may be 5–10×. When a methamphetamine-using PWID emerges from a multi-day run, the 12–24 hour PEP window has long closed. Multiple parenteral exposures may have occurred. Multiple sexual exposures may have occurred. There is no point from which to count the window because the window closed repeatedly throughout the run.

Critically, no medication-assisted treatment exists for methamphetamine use disorder. For opioid use disorder, methadone and buprenorphine provide stabilization that can facilitate engagement with HIV prevention services. For methamphetamine, no pharmacological equivalent exists. Behavioral interventions (contingency management) show modest efficacy but poor retention. The methamphetamine-using PWID is beyond the reach of current treatment infrastructure.

The Incarceration-Infection Loop

The United States incarcerates PWID at rates unparalleled in the developed world. Possession of controlled substances and paraphernalia are criminal offenses in most jurisdictions. The predictable consequence is a cycling of PWID through carceral facilities that systematically increases HIV risk:

During incarceration:

- Medication-assisted treatment unavailable in >90% of facilities
- PrEP: Not available (not approved for PWID regardless)
- Forced abstinence without treatment → tolerance reset
- No discharge planning or care continuity

Upon release:

- Relapse rate: $\sim$85%
- Tolerance reset $\rightarrow$ overdose risk elevated 12.7$\times$ in first week
- No prescription bridge
- No healthcare connection
- No housing
- Return to injection drug use $\rightarrow$ return to HIV exposure

The felony conviction creates permanent economic exclusion: employment barriers, housing disqualification, ineligibility for public assistance. With legal income inaccessible, survival options narrow to the drug economy and sex work—both carrying elevated HIV exposure risk.

The Survival Sex Work Convergence

Economic exclusion forces predictable behavioral adaptations. When legal employment is inaccessible due to felony record, when housing assistance is barred, when SNAP benefits are denied, the calculus of survival reduces to available options: return to drug distribution (re-arrest risk) or exchange of sex for money/drugs (infection risk).

Survival sex work compounds the risk architecture:

- Multiple sexual partners per day/week
- Condom negotiation power: minimal (economic desperation)
- Premium payment for condomless sex $\rightarrow$ economic incentive for risk
- Methamphetamine use to sustain activity $\rightarrow$ judgment impairment
- Violence risk with no recourse to law enforcement
- PrEP: Not accessible (no continuity of care, stigma, cost)
- PEP: Window missed by definition (continuous exposure)

The combination of injection drug use, methamphetamine, survival sex work, and post-incarceration status creates a population for whom HIV infection is not a risk but a mathematical certainty given sufficient time. The only variable is how quickly $R(0) > 0$ is established.

Manufactured Death: The Formal Definition

We define *Manufactured Death* as follows:

> *Manufactured Death: The systematic creation of conditions under which the only solvable equation—$R(0) = 0$—cannot be solved for a defined population, thereby guaranteeing chronic infection, progressive morbidity, and premature mortality through policy design rather than pathogen biology.*

The term is precise, not rhetorical. Each component is demonstrable:

Systematic: The conditions are not accidental but produced by interconnected policy decisions—criminalization, incarceration, felony exclusions, regulatory omission, funding patterns—that function as a coherent system regardless of intent.

Creation of conditions: The policies actively produce the risk architecture. No FDA-approved PrEP for PWID is not a natural state but a regulatory decision maintained for 44 years. Denial of MAT in prisons is not inevitable but a policy choice. Felony exclusions from housing and employment are statutory, not biological.

The only solvable equation: $R(0) = 0$ is mathematically the only closed-form solution. This is not opinion but theorem.

Cannot be solved: For PWID, $P(\text{achieving } R(0) = 0 \mid \text{current system}) \approx 0$. No PrEP approval, impossible PEP timing, no harm reduction infrastructure at scale.

Defined population: PWID are identifiable, enumerable ($\sim$3.5 million in the United States), and distinguished by a specific exposure route that compresses the PEP window beyond system capability.

Policy design rather than pathogen biology: HIV is preventable. The Prevention Theorem proves this. The failure is not biological—we have PrEP agents that work—but political. The agents are not approved for PWID. The infrastructure does not exist to deliver them.

Discussion

The master equation for HIV reservoir dynamics has one closed-form solution: $R(0) = 0$. All other approaches—treatment, cure strategies, therapeutic interventions—operate on the $R(0) > 0$ condition and cannot achieve $R(t) = 0$ from that starting point. The equation does not permit it.

For people who inject drugs, current policy renders $R(0) = 0$ mathematically unachievable:

- No FDA-approved pre-exposure prophylaxis
- Post-exposure prophylaxis window (12–24 hours) structurally impossible to meet
- Harm reduction infrastructure absent or underfunded
- Incarceration-release cycle systematically amplifies risk
- Economic exclusion forces survival behaviors with elevated exposure
- Methamphetamine epidemic accelerating transmission beyond reach of intervention

This is not failure of the healthcare system. This is function. The system is operating as designed—designed by policies that criminalize addiction, exclude the convicted, deny evidence-based treatment, and withhold prevention from those who need it most.

We have named this *Manufactured Death* because precision matters. The deaths are not natural consequences of pathogen biology. They are manufactured—produced by human decisions, encoded in statute and regulation, maintained by political choice, and renewed each year that PURPOSE 4 remains the first and only prevention trial for PWID in the 44-year history of the epidemic.

The Prevention Theorem will remain true regardless of policy. $R(0) = 0$ will remain the only solution. The question is whether we will create conditions under which that solution can be achieved—or whether we will continue to manufacture the alternative.

Every infection in a population denied prevention is not an epidemic outcome. It is a policy outcome. And policy can change.

The mathematics are clear. The choice is ours.

Declarations

Competing Interests: The author declares no competing financial interests. The author has previously been employed by Gilead Sciences, Inc., manufacturer of Truvada, Descovy, and Yeztugo. This manuscript was developed independently without input from or review by Gilead Sciences.

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Data Availability: All simulation code is available upon publication. The master equation and PEP efficacy models are fully specified in the Methods section and can be independently implemented.

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