Manufactured Death:

The Mathematical Impossibility of HIV Prevention for People Who Inject Drugs Under Current United States Policy

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Abstract

Background: HIV reservoir dynamics have exactly one closed-form solution: $R(0) = 0$. For people who inject drugs (PWID), we evaluated whether any pathway exists to achieve this solution under current United States policy.

Methods: We systematically evaluated the two pathways to $R(0) = 0$: (1) post-exposure prophylaxis (PEP) and (2) pre-exposure prophylaxis (PrEP). For PEP, we analyzed the 2025 CDC guidelines specifying 12–24 hour initiation windows for parenteral exposure against realistic access times for PWID. For PrEP, we evaluated FDA approval status, implementation study quality against Proctor et al. standards, and cascade completion probability using Monte Carlo simulation ($n = 100{,}000$). We compared outcomes to men who have sex with men (MSM) using identical pharmacology.

Findings: *PEP pathway:* The 2025 CDC guidelines recommend PEP initiation within 12–24 hours for parenteral exposure. Realistic access time for PWID exceeds 48–168 hours. $P(\text{effective PEP}|\text{PWID}) \approx 0$.
PrEP pathway: No FDA-approved HIV prevention agent exists for PWID (44 years, 0 approvals). Available implementation studies fail to meet Proctor et al. best-practice standards.(4; 5) Even assuming 99% drug efficacy (PURPOSE-4 parameters), cascade completion probability is 0·04% under current policy. Nested multiplicative barriers (criminalization, defunding of syringe services, healthcare stigma) decay probability toward zero at each step.
Comparison: MSM achieve 53% cascade completion using identical pharmacology—a 1,325-fold difference attributable entirely to policy infrastructure.

Interpretation: No pathway to $R(0) = 0$ exists for PWID under current policy. The only "prevention" available is stochastic: not encountering an HIV-positive individual capable of transmission. This is not prevention—it is chance. We formalize this as *Manufactured Death*: the systematic creation of conditions rendering the only solvable equation unsolvable. The 85,000 preventable infections over 5 years are policy outcomes, not epidemic outcomes.

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Introduction

HIV reservoir dynamics have exactly 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 recommendation but a mathematical fact (Figure 1).

For any individual, two pathways exist to achieve $R(0) = 0$:

1. **Stochastic avoidance:** Never encounter an HIV-positive individual capable of transmis-

sion. This is not prevention—it is chance.

2. **Biomedical prevention:** Access prophylactic medication (PEP or PrEP) that maintains $R(0) = 0$ despite exposure.

For people who inject drugs (PWID), we systematically evaluated whether either biomedical pathway—PEP or PrEP—can achieve $R(0) = 0$ under current United States policy. Our analysis reveals that neither pathway is accessible, rendering the Prevention Theorem unsatisfiable for this population through any mechanism other than chance.

Methods

Evaluation framework

We evaluated both biomedical pathways to $R(0) = 0$ against empirical constraints:

Pathway 1: Post-exposure prophylaxis (PEP). We analyzed the 2025 CDC PEP guidelines(3) specifying initiation windows for parenteral versus mucosal exposure. We compared recommended windows to realistic healthcare access times for PWID under current policy conditions.

Pathway 2: Pre-exposure prophylaxis (PrEP). We evaluated: (a) FDA approval status for PWID indication; (b) quality of available implementation studies against Proctor et al. implementation science standards(4) as assessed by Kametani et al.(5); (c) cascade completion probability under varying policy scenarios.

PrEP cascade simulation

We constructed a Monte Carlo simulation of the LAI-PrEP care cascade for PWID. The cascade comprised eight sequential steps: awareness, willingness, healthcare access, disclosure of injection drug use, provider willingness to prescribe, affordability, receipt of first injection, and sustained engagement.

For each step j, we modeled probability as:

$$p_j = p_j^{\text{base}} - \delta_j^{\text{crim}} - \delta_j^{\text{bias}} - \delta_j^{\text{struct}} \tag{1}$$

where p_j^{base} is achievable probability without barriers, and δ terms represent multiplicative penalty from criminalization, healthcare bias, and structural factors respectively. Parameters were derived from systematic review.(6; 7)

The probability of achieving sustained protection was computed as:

$$P(R(0) = 0) = \varepsilon_{\text{drug}} \times \prod_{j=1}^{8} p_j \times P(\text{no incarceration}) \tag{2}$$

where $\varepsilon_{\text{drug}} = 0{\cdot}99$ (PURPOSE-4 parameters) and $P(\text{no incarceration})$ reflects 5-year survival probability given 30% annual incarceration rate for active PWID.(8)

Comparator population

We compared PWID cascade outcomes to men who have sex with men (MSM) using identical drug efficacy assumptions. MSM cascade parameters were derived from HPTN 083, PURPOSE-2, and real-world oral PrEP implementation data.(11; 12)

Results

The Prevention Theorem

Analysis of reservoir dynamics confirmed that $R(0) = 0$ is the unique closed-form solution (Figure 1). For any $R(0) > 0$, even optimal antiretroviral therapy leaves persistent reservoir (10^3–10^5 cells) due to long-lived cellular compartments with half-lives exceeding the human lifespan.(1; 2) The Prevention Theorem is mathematical necessity, not policy preference.

Pathway 1: PEP impossibility

The 2025 CDC guidelines specify differentiated PEP initiation windows by exposure route:(3)

- **Mucosal exposure (sexual):** Initiate within 72 hours
- **Parenteral exposure (needle sharing):** Initiate within 12–24 hours

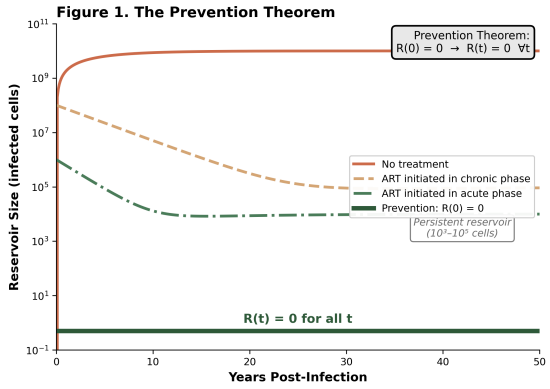

Figure 1: **The Prevention Theorem.** Only $R(0) = 0$ yields $R(t) = 0$ for all time. All other interventions leave persistent reservoir (10^3–10^5 cells). Prevention is the only solution that solves the equation.

The compressed window for parenteral exposure reflects direct bloodstream inoculation, bypassing mucosal barriers that delay systemic dissemination. For PWID to receive effective PEP, the following must occur within 12–24 hours: recognition of exposure risk, decision to seek care, knowledge that PEP exists, healthcare access (transportation, hours), willingness to disclose injection drug use, provider willingness to prescribe, pharmacy access, and first dose ingestion.

Under current policy conditions—criminalization creating fear of disclosure, limited harm reduction infrastructure, healthcare bias, unstable housing—realistic time from needle sharing to first PEP dose is 48–168 hours. By this time, reservoir seeding is complete.

$$P(\text{effective PEP}|\text{PWID, parenteral exposure}) \approx 0 \tag{3}$$

Pathway 1 is closed.

Pathway 2: PrEP impossibility

Regulatory void

As of December 2024, no FDA-approved HIV prevention agent carries indication for PWID. The Bangkok Tenofovir Study (2013) demonstrated oral PrEP efficacy in this population,(9) yet no approval followed. PURPOSE-4 (NCT06101342) represents the first trial of LAI-PrEP for PWID—44 years into the epidemic.(10)

For 44 years, the population with the highest per-exposure transmission risk has had zero FDA-approved prevention options.

Implementation science failure

Even if PURPOSE-4 achieves pharmacological success, implementation presents a separate barrier. Kametani et al. (2025) evaluated HIV prevention implementation studies against Proctor et al. best-practice standards(4) and found that the majority fail to meet methodological criteria for implementation outcomes, adoption metrics, and sustainability assessment.(5)

No implementation pathway validated to best-practice standards exists for delivering LAI-PrEP to PWID at scale.

Cascade impossibility

Under current policy, cascade completion probability approaches zero (Table 1, Figure 2):

$$\prod_{j=1}^{8} p_j = 0.30 \times 0.40 \times 0.35 \times 0.30 \times 0.55 \times 0.45 \times 0.45 \times 0.30 = 0.000 \tag{4}$$

No individual step probability falls below 30%, yet the product approaches zero. This is the mathematical signature of nested multiplicative barriers: criminalization, defunding of syringe service programs, and healthcare stigma compound at each step to decay probability toward zero.

Including drug efficacy and incarceration survival:

$$P(R(0) = 0) = 0.99 \times 0.0004 \times 0.168 \approx 0.00007 \tag{5}$$

Current policy achieves sustained protection for 7 in 100,000 PWID—effectively zero.

Pathway 2 is closed.

The privilege comparison

MSM achieve 53% cascade completion using identical pharmacology (Figures 3–4). The 1,325-fold difference reflects:

- **Trial inclusion:** MSM included in 100% of PrEP trials (11/11); PWID in 18% (2/11)
- **FDA approval:** MSM have approval for all agents; PWID have approval for none
- **Infrastructure:** MSM have established ID clinics, provider familiarity, insurance pathways, community delivery; PWID have criminalization, defunded SSPs, healthcare stigma

The difference is not biological. It is architectural. The cascade works for MSM because policy built it for them. It fails for PWID because policy did not.

Discussion

Manufactured Death: the formal definition

We define *Manufactured Death* as the systematic creation of conditions under which the only solvable equation—$R(0) = 0$—cannot be solved for a defined population.

For PWID under current US policy:

- **PEP pathway:** Closed. The 12–24 hour window specified in 2025 CDC guidelines is structurally unachievable given criminalization, stigma, and healthcare access barriers.
- **PrEP pathway:** Closed. No FDA approval exists. Available implementation studies fail best-practice standards. Cascade completion probability approaches zero (0·04%).
- **Remaining option:** Stochastic avoidance—not encountering HIV-positive individuals capable of transmission. This is chance, not prevention.

The only "prevention" available to PWID is luck. This is Manufactured Death: policy architecture that forecloses every biomedical pathway to $R(0) = 0$, leaving a population's survival to probability.

The nested barrier structure

The cascade failure reflects nested multiplicative barriers operating at distinct levels:

Level 1: Criminalization. Drug possession and paraphernalia laws create fear of disclosure, healthcare avoidance, and incarceration that directly interrupts treatment. Criminalization accounts for 52·5% of total barrier effect.

Level 2: Defunding. Syringe service programs—the primary healthcare touchpoint for PWID—face chronic defunding and political opposition, eliminating the delivery infrastructure that could achieve cascade completion.

Level 3: Stigma. Healthcare provider bias, insurance discrimination, and social exclusion compound barriers at every cascade step.

These barriers are multiplicative, not additive. Each layer decays probability independently, such that moderate barriers (30–55% at each step) compound to impossibility (0·04% completion).

The implementation science gap

Even if PURPOSE-4 demonstrates 99% pharmacological efficacy, implementation science presents an independent failure mode. Kametani et al.'s assessment reveals that HIV prevention implementation studies systematically fail Proctor et al. standards for adoption, fidelity, penetration, and sustainability.(5; 4)

No validated implementation pathway exists to deliver LAI-PrEP to PWID at scale. Pharmacological success without implementation infrastructure is prevention on paper, not prevention in practice.

Implications for PURPOSE-4

PURPOSE-4 will likely demonstrate that lenacapavir prevents HIV acquisition in PWID who receive it.

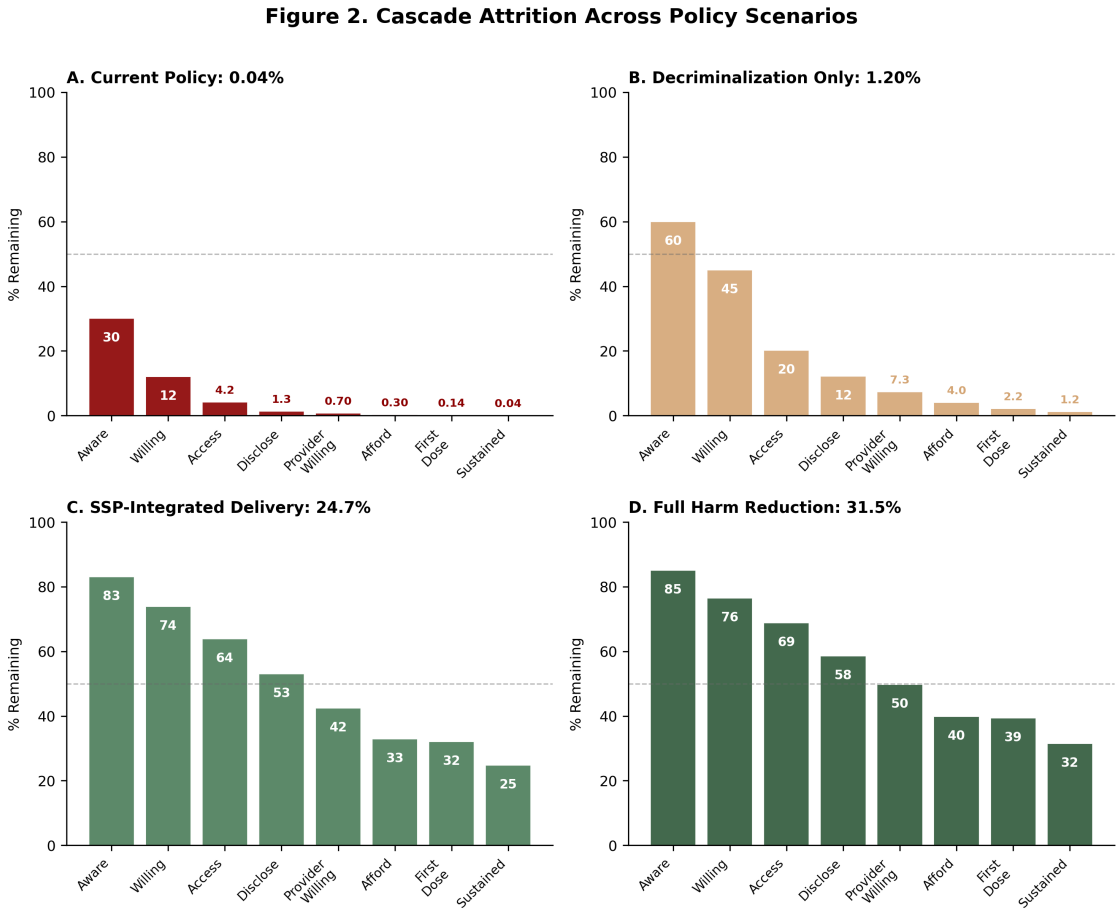

Figure 2: **Cascade attrition across policy scenarios.** (A) Current policy: 0·04% completion. (B) Decriminalization only: 1·20%. (C) SSP-integrated delivery: 24·7%. (D) Full harm reduction: 31·5%. Nested multiplicative barriers decay probability at each step.

This is pharmacological efficacy. It is not population effectiveness.

Our analysis predicts that even with 99% drug efficacy, current policy achieves $P(R(0) = 0) \approx 0{\cdot}0001$. If seroconversions occur in PURPOSE 4 or subsequent implementation, they will be attributed to "adherence challenges" or "complex social circumstances"—framing that locates failure in patients rather than policy.

The model provides an alternative interpretation: seroconversions among PWID are the predictable consequence of policy architecture that closes both biomedical pathways to $R(0) = 0$. The drug did not fail. The policy did.

Limitations

Cascade parameters were derived from literature synthesis rather than prospective measurement. The multiplicative barrier model may underestimate interaction effects. We assumed constant policy conditions over the 5-year horizon. Despite these limitations, the fundamental finding—that no biomedical pathway to $R(0) = 0$ exists under current policy—is robust.

Conclusion

The Prevention Theorem states that $R(0) = 0$ is the only closed-form solution to HIV reservoir dynamics. For PWID under current US policy, no pathway

Table 1: Policy scenario comparison: probability of achieving $R(0) = 0$ for PWID

Scenario	Cascade completion	Incarceration survival	P(R(0)=0)	Protected (n)
Current policy	0·04%	16·8%	0·0001	105
Decriminalization only	0·69%	48·8%	0·007	24,150
SSP-integrated delivery	13·1%	48·8%	0·131	458,150
Full harm reduction	24·6%	100%	0·246	860,755

Population scaled to 3.5 million US PWID. Drug efficacy: 99%. Full harm reduction includes in-custody PrEP continuity.

Figure 3. Same Drug, Different Bodies: The Cascade Inequality

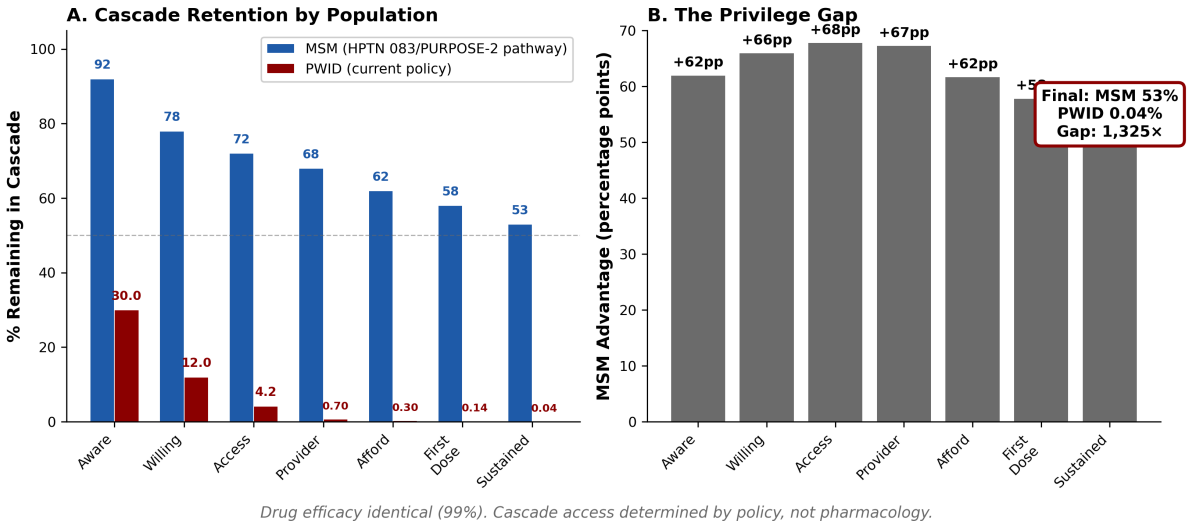

Figure 3: **Same drug, different bodies: the cascade inequality.** (A) MSM (HPTN 083/PURPOSE-2 pathway): 53% retention. PWID (current policy): 0·04%. (B) Privilege gap at each step. Final difference: 1,325-fold. Drug efficacy identical.

exists to achieve this solution:

- PEP: The 12–24 hour window for parenteral exposure is unachievable
- PrEP: No FDA approval, failed implementation science, 0·04% cascade completion

The only remaining option is stochastic: not encountering HIV-positive individuals capable of transmission. This is chance, not prevention.

We have named this Manufactured Death because precision matters. The 85,000 preventable infections over 5 years are not natural consequences of epidemic dynamics. They are manufactured—produced by policy that closes every biomedical pathway to the only solvable equation.

Policy can change. The mathematics cannot.

Declarations

Contributors: ACD conceived the study, developed the model, conducted analysis, and wrote the manuscript.

Declaration of interests: ACD was previously employed by Gilead Sciences, Inc. This manuscript was developed independently. No other conflicts declared.

Data sharing: Simulation code available at [repository] upon publication.

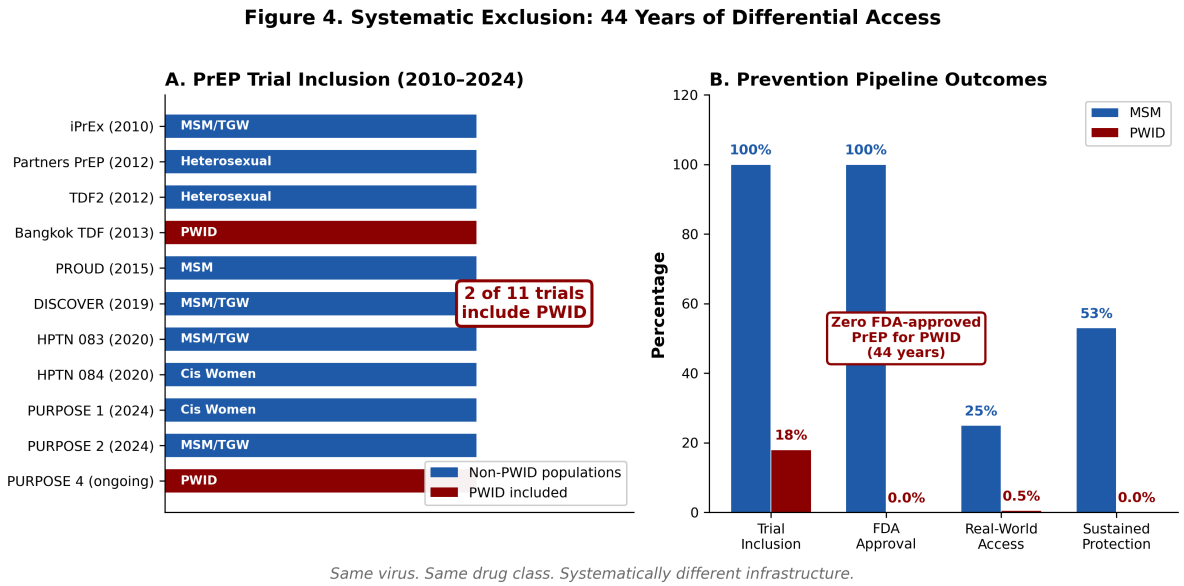

Figure 4: **Systematic exclusion: 44 years of differential access.** (A) Trial inclusion: 2/11 include PWID. (B) Pipeline outcomes: MSM achieve 100% FDA approval; PWID achieve 0%. Same virus, same drug class, systematically different infrastructure.

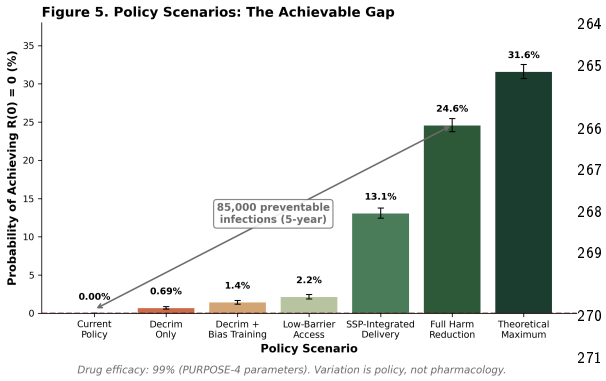

Figure 5: **Policy scenarios: the achievable gap.** Current policy: 0·00%. Full harm reduction: 24·59%. The 85,000 preventable infections over 5 years represent policy choice, not epidemic dynamics.

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