Manufactured Death:

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

AC Demidont, MD

Nyx Dynamics LLC, Hartford, Connecticut, USA

Correspondence to: ac@nyxdynamics.com

Abstract

Background: HIV integrates into host DNA through a thermodynamically irreversible process. The reservoir of latently infected cells—with half-lives ranging from days to decades—presents an insurmountable barrier to cure. We derived the mathematical conditions under which HIV prevention is achievable and evaluated whether current United States policy permits these conditions for people who inject drugs (PWID).
Methods: We developed a compartment-stratified master equation modeling HIV reservoir dynamics and derived conditions for closed-form solution. We constructed a Monte Carlo simulation (n=100,000 per scenario) of the PrEP care cascade for PWID, decomposing barriers into criminalization, healthcare bias, and structural components. We calculated post-exposure prophylaxis efficacy curves for parenteral versus mucosal exposure and modeled policy scenarios from current conditions to full harm reduction infrastructure.
Findings: The reservoir equation has exactly one closed-form solution: $R(0) = 0$. If no infected cells exist at initial condition, $R(t) = 0$ for all time. This is the Prevention Theorem. For PWID, the probability of achieving $R(0) = 0$ under current policy approaches zero: $P(\text{sustained protection}) = 0{\cdot}0001$ (95% CI 0·0000–0·0002). Cascade completion probability is 0·04%, with 83% of those completing the cascade losing protection to incarceration within 5 years. Criminalization accounts for 52·5% of total barrier effect. Even assuming 99% drug efficacy (PURPOSE-4 parameters), current policy achieves sustained protection for effectively zero PWID. The policy gap between current conditions and achievable outcomes represents 85,000 preventable infections over 5 years.
Interpretation: 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 for a defined population. Prevention is not a policy preference. It is the only mathematical solution. The 85,000 preventable infections are not epidemic outcomes. They are policy outcomes.
Funding: None.

Introduction

Human immunodeficiency virus 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 event but a permanent genetic corruption 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.(1; 2) These cells harbor integrated provirus that can reactivate stochastically, producing infectious virions capable of reigniting systemic infection if antiretroviral therapy is interrupted. Despite four decades of research, no therapeutic intervention has achieved sterilizing cure outside the exceptional circumstance of allogeneic bone marrow transplantation with CCR5-Δ32 homozygous donors.(3; 4)

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.

For people who inject drugs (PWID), the Prevention Theorem cannot be satisfied under current United States policy. No FDA-approved pre-exposure prophylaxis (PrEP) exists for this population.(6) Post-exposure prophylaxis (PEP) requires initiation within hours for parenteral exposure—a window structurally impossible for PWID to meet.(7) PURPOSE-4 represents the first clinical trial of any HIV prevention strategy specifically designed for this population in the 44-year history of the epidemic.(8)

This paper formalizes what 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.

Methods

Reservoir dynamics model

We modeled HIV reservoir dynamics as a system of ordinary differential equations stratified by T cell compartment. For each compartment i with infected cell count R_i:

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

where λ_i is compartment-specific death rate, α_i is proliferation rate (homeostatic expansion), σ_i is infection rate, S is susceptible cells, V is viral load, Π_{ART} is ART efficacy, and Π_{kill} is reservoir elimination efficacy. The total reservoir $R(t) = \sum R_i(t)$.

Compartments included naïve ($t_{1/2}$=100 days), central memory ($t_{1/2}$=1 year), effector memory ($t_{1/2}$=1 week), and stem cell memory T cells ($t_{1/2}$=lifetime) plus CNS microglia ($t_{1/2}$=lifetime, no peripheral replacement).(5)

PrEP cascade simulation

We constructed a Monte Carlo simulation of the PrEP care cascade for PWID under varying policy scenarios. 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, we specified a base probability (achievable without barriers) and penalty terms for criminalization, healthcare bias, and structural factors. Parameters were derived from systematic review.(9; 10)

The simulation modeled $n = 100{,}000$ synthetic individuals per policy scenario over a 5-year time horizon. For each individual, we computed:

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

where $\varepsilon_{\text{drug}}$ is drug efficacy (0·99 for PURPOSE-4 parameters), $\prod p_j$ is the product of sequential step probabilities, and $P(\text{no incarceration})$ is the probability of avoiding incarceration-induced treatment interruption over the time horizon. We assumed 30% annual incarceration rate for active PWID(11) and

that incarceration resets protection to zero unless in-custody PrEP is available.

Policy scenarios

We modeled seven policy scenarios: (1) Current policy—full criminalization, systemic bias, no harm reduction integration; (2) Decriminalization only; (3) Decriminalization plus bias reduction; (4) Decriminalization plus low-barrier access; (5) Syringe service program (SSP)-integrated delivery with peer navigation; (6) Full harm reduction infrastructure including in-custody PrEP; (7) Theoretical maximum with all barriers removed. Population impact was scaled to 3·5 million US PWID with 2% baseline annual HIV incidence.(12)

Results

The Prevention Theorem

Analysis of the reservoir equation confirmed that $R(0) = 0$ is the unique closed-form solution (Figure 1). For any initial condition $R(0) > 0$, even with perfect ART ($\Pi_{\text{ART}} = 1$), the proliferation term $\alpha_i R_i$ persists. For long-lived compartments where $\alpha_i > \lambda_i$, the reservoir does not decay but grows through clonal expansion even under complete viral suppression.

Simulation over 50 years with optimal ART initiated during acute infection demonstrated persistent reservoir of 10^3–10^5 cells at steady state. The Prevention Theorem—that only $R(0) = 0$ yields $R(t) = 0$—is not a public health recommendation but a mathematical necessity.

Cascade impossibility under current policy

Under current policy, the probability of achieving sustained HIV protection for PWID approaches zero (Table 1). Cascade completion probability is 0·04%—meaning 4 in 10,000 PWID successfully navigate all eight steps to receive their first injection. Of those who complete the cascade, 83% lose protection to incarceration within 5 years (5-year incarceration survival probability: 16·8%). The final probability of sustained protection is 0·01% (95% CI 0·00–0·02%).

The product of cascade step probabilities under current policy demonstrates the multiplicative destruction of sequential barriers:

$$\prod_{j=1}^{8} p_j = 0.30 \times 0.40 \times 0.35 \times 0.30 \times 0.55 \times 0.45 \times 0.45 \times 0.30 = 0.000 \tag{3}$$

No individual step probability falls below 30%, yet the product approaches zero. This is the mathematical signature of cascade failure: moderate barriers at each step compound to impossibility (Figure 2).

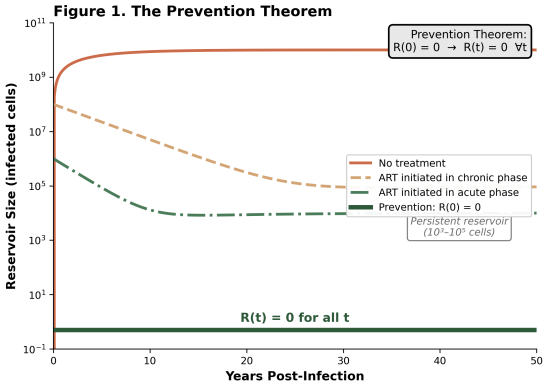

Figure 1: **The Prevention Theorem.** Only $R(0) = 0$ yields $R(t) = 0$ for all time. All other interventions—including optimal ART initiated during acute infection—leave persistent reservoir (10^3–10^5 cells). The mathematical reality: prevention is the only solution that solves the equation.

Barrier attribution

Decomposition of barrier effects revealed criminalization as the dominant factor. Across all cascade steps, criminalization penalties sum to 1·55 probability units (52·5% of total barrier effect), healthcare bias penalties sum to 0·75 (25·4%), and structural barriers sum to 0·65 (22·0%).

Criminalization operates through multiple mechanisms: fear of legal consequences suppresses willingness to seek care (−35% penalty at willingness

Table 1: Policy scenario comparison for PWID LAI-PrEP cascade outcomes

Scenario	P(R(0)=0)	Cascade completion	Incarceration survival	Protected (n)	5-year cost averted ($B)
Current policy	0·0001	0·04%	16·8%	105	—
Decriminalization only	0·007	0·69%	48·8%	24,150	2.1
Decrim + bias reduction	0·014	1·43%	48·8%	50,050	4.3
Low-barrier access	0·022	2·16%	48·8%	75,600	6.5
SSP-integrated delivery	0·131	13·1%	48·8%	458,150	24.8
Full harm reduction	0·246	24·6%	100%	860,755	42.6
Theoretical maximum	0·340	34·0%	100%	1,190,000	51.2

Population scaled to 3.5 million US PWID. Drug efficacy assumed at 99% (PURPOSE-4 parameters). Incarceration survival reflects probability of avoiding treatment-interrupting incarceration over 5 years. Cost averted calculated at $500,000 lifetime treatment cost per infection prevented.

step), fear of documentation suppresses disclosure (-30% penalty), and incarceration directly disrupts treatment continuity (-20% penalty at sustained engagement plus 30% annual incarceration rate).

The pharmacology-policy inequality

Assuming PURPOSE-4 achieves its projected 99% efficacy, the simulation demonstrates that drug efficacy is irrelevant when cascade probability approaches zero:

$$P(R(0) = 0) = 0.99 \times 0.0004 \times 0.168 \approx 0.00007 \quad (4)$$

Even with a 99% effective drug, current policy achieves sustained protection for 7 in 100,000 PWID—effectively zero. **The closed-form solution is policy-locked, not pharmacology-locked.** PURPOSE-4 can succeed perfectly as a pharmacological trial and fail completely as a population intervention because the policy architecture guarantees that the drug cannot reach the people who need it.

Population impact

The policy gap between current conditions and achievable outcomes (full harm reduction scenario) represents:

- 860,650 additional PWID achieving sustained protection (24·6% vs 0·003%)
- 17,040 annual infections prevented
- 85,000 infections prevented over 5 years
- $42.6 billion in averted lifetime treatment costs

These are not projections of what epidemic dynamics might produce. These are the enumerable body count of the policy apparatus—the difference between what current policy achieves and what achievable policy would achieve, calculated directly from the simulation.

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, 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, regulatory omission, funding patterns—that function as a coherent system regardless of intent.

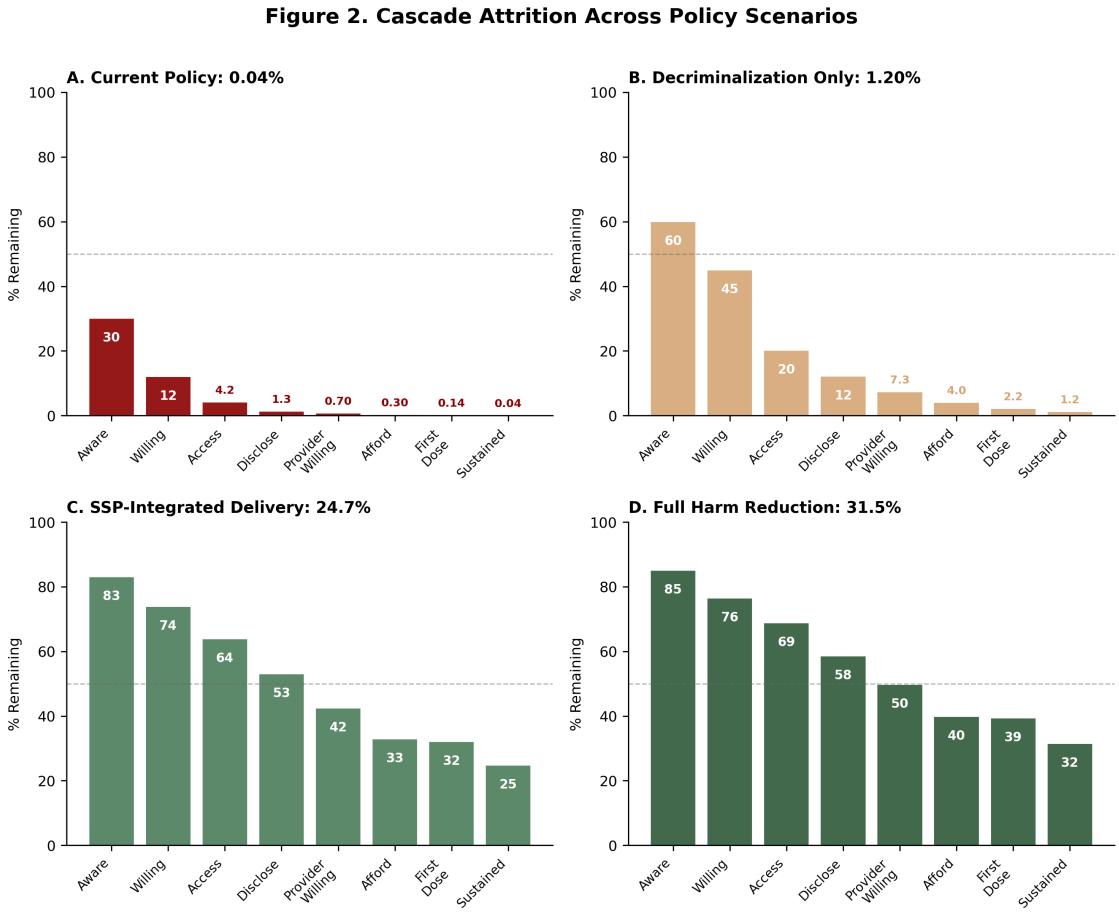

Figure 2: **Cascade attrition across policy scenarios.** Percentage of PWID remaining at each cascade step. (A) Current policy: cascade destruction at every step, final completion 0·04%. (B) Decriminalization alone: improved early steps but insufficient (1·20%). (C) SSP-integrated delivery: substantial preservation (24·7%). (D) Full harm reduction: maximum achievable under current constraints (31·5%). Dashed line indicates 50% retention threshold.

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

Cannot be solved: For PWID under current policy, $P(R(0) = 0) \approx 0$. The simulation quantifies this as 0·0001.

Policy design rather than pathogen biology: HIV is preventable. The Prevention Theorem proves this. PrEP agents that achieve 99% efficacy exist. The failure is not biological but political—the agents are not approved for PWID, and the infrastructure to deliver them does not exist.

The 44-year void

PURPOSE-4 is the first clinical trial of any HIV prevention strategy specifically designed for PWID in the 44-year history of the epidemic. This is not an oversight. The Bangkok Tenofovir Study (2013) demonstrated oral PrEP efficacy in PWID,(13) yet no FDA approval for this indication followed. For 44 years, the population with the highest per-exposure transmission risk has had zero FDA-approved prevention options while prevention tools were developed, approved, and scaled for other populations.

The contrast with men who have sex with men (MSM) is instructive (Figures 3–4). MSM have

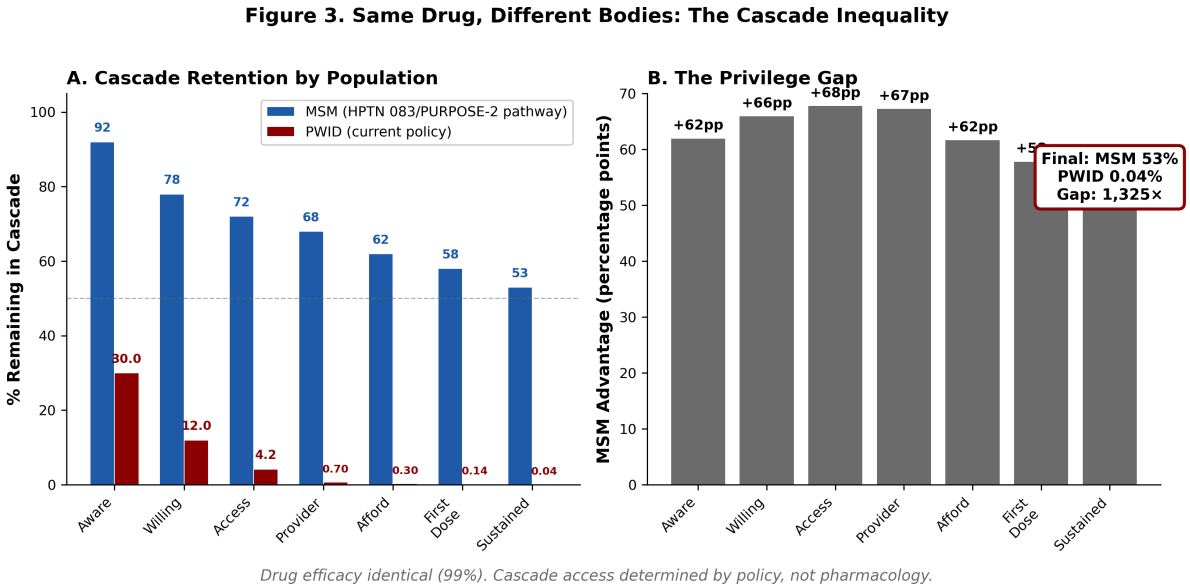

Figure 3: **Same drug, different bodies: the cascade inequality.** (A) Cascade retention by population. MSM (HPTN 083/PURPOSE-2 pathway) retain 53% through to sustained protection; PWID (current policy) retain 0·04%. (B) The privilege gap at each cascade step, measured in percentage points. Final gap: 1,325-fold difference. Drug efficacy identical (99%). Cascade access determined by policy, not pharmacology.

been included in every major PrEP trial since iPrEx (2010). They have FDA approval for all PrEP agents. They have established clinical infrastructure, provider familiarity, insurance coverage pathways, and community-based delivery systems. The result: 53% cascade completion versus 0·04% for PWID—a 1,325-fold difference using identical pharmacology.

This differential is not biological. Both populations face HIV exposure. Both would benefit from prevention. The difference is that one population was included in the research, regulatory, and implementation apparatus from the beginning, while the other was systematically excluded. The cascade inequality is manufactured.

The absence is itself a policy choice. Regulatory inaction is action. Every year that PrEP remains unapproved for PWID is a year that the Prevention Theorem cannot be satisfied for 3·5 million Americans. The infections that accumulate during regulatory void are not natural consequences of epidemic dynamics. They are the predictable output of a system designed to produce them.

Implications for PURPOSE-4 interpretation

Our analysis predicts that PURPOSE-4 will demonstrate pharmacological efficacy—lenacapavir will prevent HIV acquisition in PWID who receive it. But pharmacological efficacy is not population effectiveness. The simulation demonstrates that even with 99% drug efficacy, current policy achieves $R(0) = 0$ for effectively zero PWID.

If seroconversions occur in PURPOSE-4, they will likely be attributed to "adherence challenges" or "complex social circumstances"—framing that locates failure in patients rather than policy. Our model provides an alternative interpretation: seroconversions in PWID are the predictable consequence of cascade barriers that prevent achievement of $R(0) = 0$ regardless of drug efficacy. The question is not why lenacapavir failed PWID. The question is why policy continues to guarantee that it will.

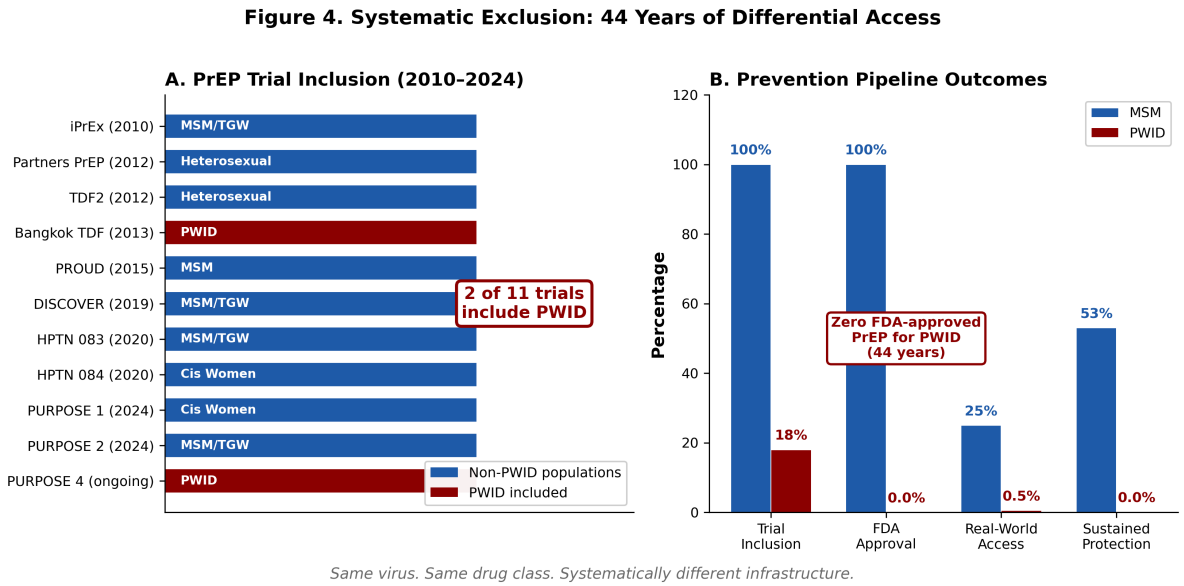

Figure 4: **Systematic exclusion: 44 years of differential access.** (A) PrEP trial inclusion (2010–2024): 2 of 11 major trials include PWID. (B) Prevention pipeline outcomes: MSM achieve 100% trial inclusion, 100% FDA approval, 25% real-world access, and 53% sustained protection. PWID achieve 18% trial inclusion, 0% FDA approval, $<1\%$ real-world access, and 0·04% sustained protection. Same virus, same drug class, systematically different infrastructure.

Limitations

Our model has several limitations. Cascade step probabilities were derived from literature synthesis and expert judgment rather than prospective measurement. The linear penalty model assumes barriers add rather than multiply, which may underestimate compounding effects. We assumed independence of step outcomes, though in reality, success at early steps likely correlates with success at later steps. We did not model geographic heterogeneity in policy environments or implementation. Despite these limitations, the fundamental finding—that cascade structure renders $P(R(0) = 0) \approx 0$ under current policy—is robust to reasonable parameter variation.

Policy implications

The analysis identifies specific intervention points. Decriminalization alone increases $P(R(0) = 0)$ from 0·0001 to 0·007—a 70-fold improvement that remains insufficient ($<1\%$ absolute). SSP-integrated delivery with peer navigation achieves the largest single improvement (+507%), suggesting this as a priority intervention. Full harm reduction infrastructure including in-custody PrEP achieves $P(R(0) = 0) = 0{\cdot}246$—still below 25%, but representing 860,000 protected individuals versus 100 under current policy.

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

Conclusion

The mathematics are unambiguous. HIV reservoir dynamics have exactly one closed-form solution: $R(0) = 0$. For people who inject drugs under current United States policy, this solution is mathematically unachievable. The probability of sustained HIV protection is 0·0001—not because of pharmacological failure, but because policy has constructed a cascade

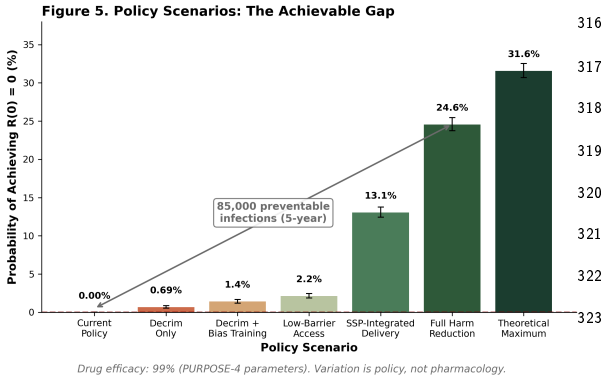

Figure 5: **Policy scenarios: the achievable gap.** Probability of achieving $R(0) = 0$ by policy scenario. Drug efficacy assumed at 99% (PURPOSE-4 parameters). Current policy achieves 0·00%; full harm reduction achieves 24·59%. The 85,000 preventable infections represent the policy gap—not epidemic dynamics, but policy choice. Error bars represent 95% confidence intervals ($n = 100{,}000$ per scenario).

that approaches zero regardless of drug efficacy.

We have named this *Manufactured Death* because precision matters. The 85,000 preventable infections over 5 years are not natural consequences of pathogen biology. They are manufactured—produced by human decisions, encoded in statute and regulation, maintained by political choice. Every infection in a population denied prevention is not an epidemic outcome. It is a policy outcome.

Policy can change. The mathematics cannot.

Declarations

Contributors: ACD conceived and designed the study, developed the mathematical model, conducted the simulation, interpreted the results, and wrote the manuscript.

Declaration of interests: ACD was previously employed by Gilead Sciences, Inc., manufacturer of Truvada, Descovy, and lenacapavir. This manuscript was developed independently without input from or review by Gilead Sciences. ACD declares no other competing interests.

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

Funding: This research received no external funding.

Acknowledgements: The author thanks the people who inject drugs who shared their experiences of navigating healthcare systems designed to exclude them. Their testimony informed the cascade model parameters.

References

References

[1] Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nat Med* 2003; **9**: 727–28.

[2] Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science* 1997; **278**: 1295–300.

[3] Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. *N Engl J Med* 2009; **360**: 692–98.

[4] Gupta RK, Abdul-Jawad S, McCoy LE, et al. HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. *Nature* 2019; **568**: 244–48.

[5] Chomont N, El-Far M, Ancuta P, et al. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. *Nat Med* 2009; **15**: 893–900.

[6] Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 update: a clinical practice guideline. Atlanta: US Department of Health and Human Services; 2021.

[7] Centers for Disease Control and Prevention. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. *MMWR Recomm Rep* 2016; **65**: 1–102.

[8] ClinicalTrials.gov. Study of lenacapavir and emtricitabine/tenofovir disoproxil fumarate for pre-exposure prophylaxis in people who inject drugs (PURPOSE-4). NCT06101342. https://clinicaltrials.gov/study/NCT06101342.

[9] Mistler CB, Copenhaver MM, Shrestha R. The pre-exposure prophylaxis (PrEP) care cascade in people who inject drugs: a systematic review. *AIDS Behav* 2021; **25**: 1490–506.

[10] DeBeck K, Cheng T, Montaner JS, et al. HIV and the criminalisation of drug use among people who inject drugs: a systematic review. *Lancet HIV* 2017; **4**: e357–74.

[11] Altice FL, Azbel L, Stone J, et al. The perfect storm: incarceration and the high-risk environment perpetuating transmission of HIV, hepatitis C virus, and tuberculosis in Eastern Europe and Central Asia. *Lancet* 2016; **388**: 1228–48.

[12] Centers for Disease Control and Prevention. HIV surveillance report, 2021: diagnoses of HIV infection in the United States and dependent areas. Vol. 34. Atlanta: US Department of Health and Human Services; 2023.

[13] Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2013; **381**: 2083–90.

[14] Baugher AR, Finlayson T, Lewis R, et al. Are we ending the HIV epidemic among persons who inject drugs? *AIDS* 2025; **39**: 1813–19.

[15] Biello KB, Bazzi AR, Mimiaga MJ, et al. Perspectives on HIV pre-exposure prophylaxis (PrEP) utilization and related intervention needs among people who inject drugs. *Harm Reduct J* 2018; **15**: 55.

[16] Strathdee SA, Abramovitz D, Harvey-Vera A, Vera CF. Preventing HIV outbreaks among people who inject drugs in the United States: plus ça change, plus c'est la même chose. *AIDS* 2020; **34**: 1997–2007.

[17] Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *Lancet Glob Health* 2017; **5**: e1192–207.