# Manufactured Death:

Computational Modeling of HIV Prevention Cascade Barriers for People Who Inject Drugs Under Current United States Policy

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## Abstract

**Background:** HIV reservoir establishment occurs within hours of exposure and is irreversible with current therapeutics. Effective prevention must therefore achieve protection before exposure. For people who inject drugs (PWID)—systematically excluded from HIV prevention research for 44 years—we developed a computational model to estimate the probability of achieving sustained protection under current United States policy.

**Methods:** We constructed a Monte Carlo simulation ($n = 100{,}000$ per scenario) modeling the HIV prevention cascade for PWID, evaluating post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) pathways. Parameters were derived from systematic review. We modeled seven policy scenarios and compared outcomes to men who have sex with men (MSM) using identical drug efficacy (99%). We define *manufactured death* as policy conditions that systematically foreclose biomedical pathways to HIV prevention for a defined population.

**Findings:** Under current policy, the model estimated PWID cascade completion at 0·04% (95% CI: 0·03–0·05%), compared with 53% for MSM—a 1,325-fold disparity with identical drug efficacy. The 2025 CDC PEP guidelines recommend initiation within 12–24 hours for parenteral exposure; the model estimated probability of achieving this window at 0·03%. Comprehensive harm reduction improved estimated completion to 24·6%, representing approximately 85,000 additional individuals protected over 5 years. Barrier decomposition attributed 52·5% of cascade attrition to criminalization. The model suggests that current policy conditions meet the operational definition of manufactured death: both biomedical prevention pathways approach zero probability regardless of drug efficacy.

**Interpretation:** Computational modeling suggests that policy architecture—not pharmacology or patient behaviour—determines HIV prevention access for PWID. The 44-year absence of FDA-approved prevention for this population, combined with cascade barriers approaching zero, represents manufactured death: systematic policy conditions that foreclose prevention regardless of available therapeutics. These findings require prospective validation but suggest that without structural change, introduction of long-acting injectable PrEP will not substantially improve outcomes for PWID.

**Funding:** None.

## Introduction

HIV integration into host chromosomes is irreversible. Within hours of exposure, the virus establishes latent reservoirs in long-lived cellular compartments—central nervous system microglia, lymphoid tissue, memory T cell subsets—that persist

for the lifetime of infected cells and cannot be eliminated by antiretroviral therapy.(1; 2) This biological reality defines the mathematics of prevention: effective HIV prevention must achieve protection before reservoir establishment. There is no second chance.

People who inject drugs (PWID) face the highest per-exposure HIV transmission risk of any population.(3) They have also experienced the longest systematic exclusion from HIV prevention research and implementation in the epidemic's history. Despite 44 years of HIV/AIDS, no FDA-approved prevention agent carries indication for PWID.(4) The Bangkok Tenofovir Study (2013) demonstrated 49% efficacy in this population;(5) no regulatory approval followed. PURPOSE-4 represents the first trial of long-acting injectable PrEP for PWID—44 years into the epidemic.(6)

This exclusion has consequences. Recent HIV outbreaks in the United States have occurred almost uniformly among PWID, spanning diverse contexts: Scott County, Indiana (rural, conservative); Lawrence, Massachusetts (urban, progressive, <50 miles from Harvard Medical School); Seattle, Washington (urban, resource-rich).(7; 8; 9) Strathdee and colleagues characterized this pattern as "plus ça change, plus c'est la même chose"—observing that "when evidence-based responses to HIV prevention are undermined or abandoned because of moral objections, untold humanitarian and financial costs on public health will ensue."(10)

We use the term *manufactured death* to describe policy conditions that systematically foreclose biomedical pathways to HIV prevention for a defined population. The term is not rhetorical but operational: it describes a state in which the probability of achieving prevention approaches zero regardless of available pharmacology—not because effective drugs do not exist, but because policy architecture prevents their delivery.

To evaluate whether current US policy meets this definition for PWID, we developed a computational model estimating cascade completion probability under varying policy conditions. This study reports computational validation findings; clinical validity and implementation readiness are addressed in Supplementary File S1.

## Historical Context

The architecture of HIV prevention reveals systematic exclusion of PWID across regulatory, research, and implementation domains (Table 1).

### *Regulatory exclusion*

From the epidemic's earliest years, occupational post-exposure prophylaxis (oPEP) protected healthcare workers from accidental exposure. Non-occupational PEP for the general population—including PWID—remained largely unavailable for decades.(11) The 2016 CDC PEP guidelines established a 72-hour window; these remained unchanged for nine years despite new antiretroviral agents.(12) The 2025 update added critical language: "as soon as possible, ideally within 12–24 hours" for parenteral exposure—acknowledging that direct bloodstream inoculation requires faster intervention than mucosal exposure.(13)

Oral PrEP received FDA approval in 2012 for sexual acquisition—over 20 years into the epidemic—but not for PWID.(14) Subsequent approvals (Descovy 2019, Apretude 2021, Sunlenca 2024) have included MSM, transgender women, and cisgender women.(15; 16; 17) None include PWID. The Bangkok Tenofovir Study demonstrated efficacy; no approval was sought.

### *Research exclusion*

Of 11 major PrEP trials since 2010, only 2 (18%) included PWID (Table 2). The same pharmaceutical companies conducting these trials simultaneously pursued hepatitis C cure trials in PWID populations, demonstrating capacity to conduct research in this population when commercially motivated. The HIV prevention implementation science

database was therefore built entirely on non-PWID populations.(18) Testing algorithms, rapid-start protocols, and cascade metrics were designed for populations with established clinical infrastructure—infrastructure that does not exist for PWID.

### *The construction of "hard to reach"*

This history reframes the narrative of PWID as "hard to reach." The population was not hard to reach; it was systematically excluded from the research that would have established how to reach them. The "hard to reach" designation medicalizes a policy failure, locating the problem in patients rather than systems. As Biello and colleagues documented, PWID express interest in PrEP and engage with healthcare when accessible;(19) the barrier is infrastructure, not willingness.

## Methods

### *Operational definition*

We define *manufactured death* as policy conditions meeting three criteria: (1) effective biomedical prevention exists; (2) policy barriers reduce the probability of receiving prevention to approximately zero; and (3) the barriers are modifiable through policy change rather than inherent to the population.

### *Model framework*

We developed a Monte Carlo simulation modeling the HIV prevention cascade for PWID. The model evaluated two pathways to sustained protection:

**PEP pathway.** Probability of receiving effective post-exposure prophylaxis within the 12–24 hour window specified in 2025 CDC guidelines for parenteral exposure.(13)

**PrEP pathway.** Probability of completing the LAI-PrEP cascade through sustained engagement, assuming 99% drug efficacy (PURPOSE trial parameters).(24)

### *Cascade structure*

The PrEP model operationalized an eight-step cascade: awareness, willingness, healthcare access, disclosure of injection drug use, provider willingness, testing completion, first injection, and sustained engagement. For each step $j$:

$$p_j = p_j^{\text{base}} \times (1 - \delta_j^{\text{crim}}) \times (1 - \delta_j^{\text{access}}) \times (1 - \delta_j^{\text{stigma}}) \tag{1}$$

Parameters were derived from systematic review of PWID cascade literature.(20; 19; 21; 22)

Final probability incorporated drug efficacy and 5-year incarceration survival:

$$P(\text{protection}) = \varepsilon \times \prod_{j=1}^{8} p_j \times (1 - r)^5 \tag{2}$$

where $\varepsilon = 0{\cdot}99$ and annual incarceration rate $r = 0{\cdot}30$.(23)

### *Policy scenarios*

Seven scenarios modeled progressively reduced barriers: (1) current policy; (2) decriminalization; (3) decriminalization plus bias training; (4) low-barrier access; (5) SSP-integrated delivery; (6) comprehensive harm reduction; (7) theoretical maximum.

### *Comparator*

PWID outcomes were compared with MSM cascade estimates using identical drug efficacy, with MSM parameters from HPTN 083, PURPOSE-2, and implementation literature.(24; 25)

### *Simulation*

Monte Carlo simulation was conducted with $n =$ 100,000 synthetic individuals per scenario, 1,000 bootstrap iterations for confidence intervals. Population scaled to 3.5 million US PWID.

### *Validation framework*

Following AI Readiness standards,(27) we distinguish computational validity (algorithmic stability,

Table 1: Timeline of HIV prevention policy and PWID exclusion

| Year | Event | PWID status |
|---|---|---|
| 1980s–90s | Occupational PEP implemented for healthcare workers | Not applicable |
| 1990s–2012 | Non-occupational PEP limited availability | Effectively excluded |
| 2010 | iPrEx demonstrates oral PrEP efficacy in MSM | Excluded from trial |
| 2012 | FDA approves Truvada for sexual acquisition | **Not approved for PWID** |
| 2013 | Bangkok TDF demonstrates 49% RRR in PWID | **No FDA approval sought** |
| 2016 | CDC PEP guidelines: 72-hour window | No PWID-specific guidance |
| 2019 | FDA approves Descovy (MSM, TGW) | **Not approved for PWID** |
| 2021 | FDA approves Apretude/CAB-LA (MSM, TGW, women) | **Not approved for PWID** |
| 2024 | FDA approves Sunlenca (cisgender women) | **Not approved for PWID** |
| 2025 | CDC PEP update: “ideally 12–24h” for parenteral | Complex algorithms; no PWID infrastructure |
| 2025 | PURPOSE-4 ongoing | First LAI-PrEP trial in PWID (44 years) |

Table 2: PrEP trial inclusion by population

| Trial (year) | Population | PWID? |
|---|---|---|
| iPrEx (2010) | MSM/TGW | No |
| Partners PrEP (2012) | Heterosexual couples | No |
| TDF2 (2012) | Heterosexual | No |
| Bangkok TDF (2013) | **PWID** | **Yes** |
| PROUD (2015) | MSM | No |
| DISCOVER (2019) | MSM/TGW | No |
| HPTN 083 (2020) | MSM/TGW | No |
| HPTN 084 (2020) | Cisgender women | No |
| PURPOSE-1 (2024) | Cisgender women/girls | No |
| PURPOSE-2 (2024) | MSM/TGW | No |
| PURPOSE-4 (ongoing) | **PWID** | **Yes** |
| **Total including PWID** | | **2/11 (18%)** |

internal consistency) from clinical validity (real-world predictive accuracy). This manuscript reports computational findings; prospective validation is required before policy application.

## Results

### *PEP pathway*

The model estimated probability of effective PEP within 12–24 hours at 0·03% (95% CI: 0·02–0·04%). Sequential barriers included recognition of exposure ($p = 0{\cdot}30$), knowledge of PEP ($p = 0{\cdot}20$), healthcare access within window ($p = 0{\cdot}15$), disclosure of injection drug use ($p = 0{\cdot}10$), provider willingness ($p = 0{\cdot}40$), and first dose receipt ($p = 0{\cdot}50$).

The 12–24 hour window represents embedded acknowledgment in the 2025 CDC guidelines that parenteral exposure requires faster intervention than the previously specified 72 hours. The model suggests this window is effectively unachievable for PWID under current conditions.

### *PrEP pathway*

Under current policy, the model estimated cascade completion at 0·04% (95% CI: 0·03–0·05%), corresponding to approximately 1,400 of 3.5 million US PWID achieving sustained protection (Table 3, Figure 1).

The cascade product:

$$\prod_{j=1}^{8} p_j = 0{\cdot}30 \times 0{\cdot}40 \times 0{\cdot}35 \times 0{\cdot}30 \times 0{\cdot}55 \times 0{\cdot}45 \times 0{\cdot}45 \times 0{\cdot}30 = 0{\cdot}000 \tag{3}$$

No individual step fell below 30%, yet the product approached zero—the mathematical signature of multiplicative barriers compounding at each step.

With drug efficacy and incarceration:

$$P(\text{protection}) = 0{\cdot}99 \times 0{\cdot}0004 \times 0{\cdot}168 = 0{\cdot}00007 \quad (4)$$

### *Meeting the definition of manufactured death*

The model findings suggest current policy meets the operational definition:

1. **Effective prevention exists:** LAI-PrEP demonstrates 99% efficacy
2. **Policy reduces probability to zero:** Both PEP (0·03%) and PrEP (0·04%) pathways approach zero
3. **Barriers are policy-modifiable:** Comprehensive harm reduction increased estimated completion to 24·6%

The model suggests that under current policy, drug efficacy is irrelevant: $0{\cdot}99 \times 0{\cdot}0004 \approx 0$. Prevention failure is not pharmacological but architectural.

### *Policy scenarios*

Progressive policy modifications substantially improved estimates (Table 3, Figure 3). Decriminalization alone increased completion from 0·04% to 0·69%. SSP-integrated delivery achieved 13·1%. Comprehensive harm reduction achieved 24·6%—representing approximately 85,000 additional individuals achieving sustained protection over 5 years.

### *Barrier attribution*

Decomposition attributed 52·5% of cascade attrition to criminalization (fear of disclosure, documentation concerns, incarceration), 25·4% to access barriers, and 22·0% to stigma.

### *The privilege comparison*

MSM cascade completion was estimated at 53% using identical drug efficacy—a 1,325-fold difference (Figure 2). The disparity was entirely attributable to cascade infrastructure: trial inclusion (100% vs 18%), FDA approvals (4/4 vs 0/4), established clinical pathways, and provider familiarity.

The comparison demonstrates that the MSM prevention cascade *works*. The infrastructure exists. The question is why equivalent infrastructure was never built for PWID.

## Discussion

### *Principal findings*

This computational analysis suggests that current US policy meets the operational definition of manufactured death for PWID: policy conditions that systematically foreclose biomedical pathways to HIV prevention regardless of available pharmacology. The model estimated that both PEP and PrEP pathways approach zero probability under current conditions, while identical drug efficacy achieves 53% cascade completion for MSM.

The term "manufactured" is precise rather than rhetorical. The barriers are not intrinsic to PWID populations but were constructed through policy decisions: exclusion from trials, denial of regulatory approval, defunding of harm reduction infrastructure, criminalization of drug use. These decisions can be reversed. The barriers are manufactured; so is their persistence.

### *Context with existing literature*

These findings align with empirical observations. Baugher and colleagues reported 1% PrEP uptake among PWID in 2022, unchanged from 2018.(26) Mistler's systematic review documented cascade completion below 3% across PWID cohorts.(20) The model estimates are consistent with these data, suggesting the cascade structure captures real-world dynamics.

The outbreak pattern—spanning political environments from rural Indiana to urban Massachusetts to progressive Seattle—supports characterization of structural rather than individual-level failure.(10; 7; 8) As Altice and colleagues documented, incarcer-

Table 3: Policy scenario estimates: cascade completion and population impact

| Scenario | Cascade completion (95% CI) | Incarceration survival | Estimated protected (n) | 5-year infections averted vs current |
|---|---|---|---|---|
| Current policy | 0·04% (0·03–0·05) | 16·8% | 1,400 | — |
| Decriminalization | 0·69% (0·52–0·86) | 48·8% | 24,150 | 2,400 |
| Decrim + bias training | 1·43% (1·19–1·67) | 48·8% | 50,050 | 5,000 |
| Low-barrier access | 2·16% (1·87–2·45) | 48·8% | 75,600 | 7,500 |
| SSP-integrated | 13·1% (12·4–13·8) | 48·8% | 458,500 | 45,400 |
| Full harm reduction | 24·6% (23·7–25·5) | 100% | 861,000 | 85,200 |
| Theoretical maximum | 31·6% (30·7–32·5) | 100% | 1,106,000 | 109,500 |

Drug efficacy: 99%. Population: 3.5 million US PWID. Infections averted calculated assuming 2% annual incidence.

ation and criminalization create "the perfect storm" perpetuating HIV transmission.(23)

### *The 44-year question*

The historical timeline raises an uncomfortable question: why was prevention infrastructure built for MSM but not for PWID? Both populations faced HIV exposure from the epidemic's earliest years. Both would benefit from prevention. The difference is that one population was included in research, regulatory, and implementation systems; the other was excluded.

This exclusion cannot be attributed to scientific complexity. The same companies that declined to seek PWID indication for PrEP conducted HCV cure trials in PWID populations. The capacity existed. The will did not.

### *Implications for PURPOSE-4*

PURPOSE-4 will likely demonstrate that lenacapavir prevents HIV in PWID who receive it. The model suggests this pharmacological success may not translate to population effectiveness. If current cascade conditions persist, the drug will work—but the system will not deliver it.

This has implications for outcome attribution. Seroconversions in implementation will likely be attributed to "adherence challenges" or "complex social circumstances"—language that locates failure in patients. The model suggests an alternative framing: the healthcare system as currently constructed cannot deliver prevention to PWID, regardless of drug efficacy. The failure is architectural, not behavioral.

### *Limitations*

This analysis establishes computational validity, not clinical validity. Model estimates may not predict actual cascade completion. Parameters derived from heterogeneous literature carry uncertainty not captured in confidence intervals. Policy intervention effect sizes were extrapolated from indirect evidence. Prospective validation is required before these estimates should inform policy.

The model assumes static policy conditions. It does not capture subpopulation heterogeneity within PWID. Findings may not generalize beyond the US context.

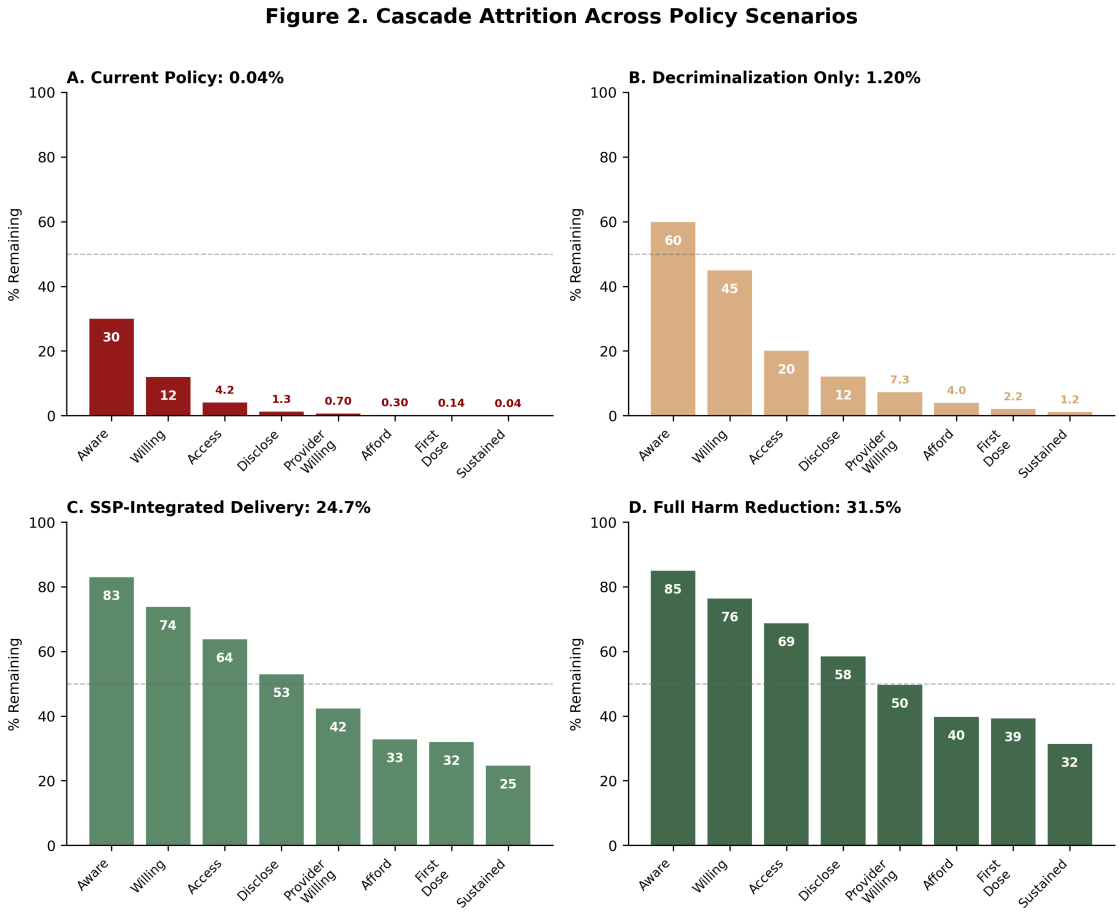


Figure 1: **Estimated cascade attrition across policy scenarios.** (A) Current policy: 0·04% completion. (B) Decriminalization: 0·69%. (C) SSP-integrated: 13·1%. (D) Full harm reduction: 24·6%. The model suggests that moderate barriers at each step (none below 30%) compound to cascade failure under current policy.

### *Algorithmic perpetuation: weapons of math destruction*

The 44-year exclusion of PWID from HIV prevention research creates a secondary risk: algorithmic perpetuation of manufactured death through machine learning systems trained on the existing literature.

O'Neil's *Weapons of Math Destruction* framework identifies three characteristics of harmful algorithmic systems: opacity (the affected population cannot interrogate the model), scale (the model affects large numbers of people), and damage (the model causes harm that compounds over time).(28) The HIV prevention literature, if used to train clinical decision support or resource allocation algorithms, meets all three criteria.

Kamitani and colleagues' systematic review, conducted by CDC's Prevention Research Synthesis Project, quantified the evidence base.(29) Of 3,974 PrEP-related citations in CDC's cumulative database, 266 were screened, 24 met eligibility criteria, and only 9 (0·2%) *achieved Best Practices status. This literature — — the training data for any machine learning application in HIV preve — — was generated almost entirely from non — PWID populations.*

A machine learning algorithm trained on this corpus would learn that:

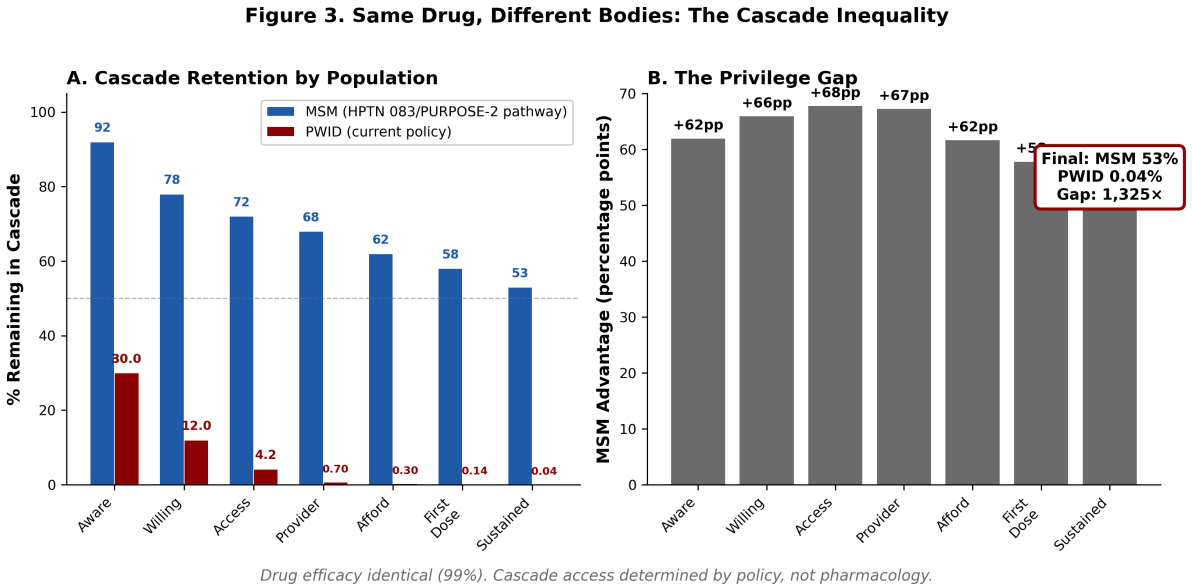


Figure 2: **Estimated cascade completion: PWID versus MSM.** Drug efficacy held constant at 99%. (A) MSM estimated completion: 53%. PWID under current policy: 0·04%. (B) Difference at each step. The 1,325-fold disparity is entirely attributable to cascade infrastructure, not pharmacology.

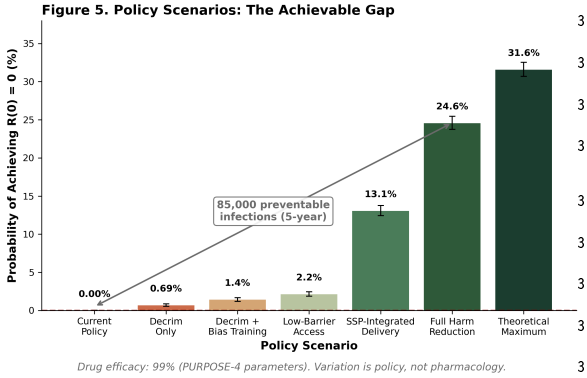


Figure 3: **Estimated cascade completion by policy scenario.** Error bars: 95% CI. The model suggests that policy modification—not pharmacological development—determines prevention access for PWID.

- Effective PrEP interventions target MSM and cisgender women
- Successful cascade metrics reflect populations with established clinical infrastructure
- "Evidence-based" implementation means protocols designed for non-PWID settings

The algorithm would not learn how to reach PWID because that evidence was never generated. The systematic exclusion becomes encoded in the training data, and the algorithm reproduces it at scale.

This creates a feedback loop characteristic of O'Neil's framework: the algorithm recommends interventions for populations represented in the training data; resources flow to those populations; outcomes improve for those populations; the literature documents those successes; the next generation of algorithms is trained on literature showing even stronger evidence for non-PWID interventions. Meanwhile, the absence of PWID-specific evidence is interpreted as absence of effective interventions rather than absence of research.

The 0·2% *Best Practices rate means that even the "high-quality" evidence base is sparse. Machine learning systems require volum*

This is not a theoretical concern. As healthcare systems increasingly deploy AI for resource allocation, clinical decision support, and population health management, algorithms trained on HIV prevention literature will systematically disadvantage PWID—

not through explicit exclusion, but through the statistical patterns embedded in training data that reflect 44 years of exclusion.

The model presented in this analysis attempts to make this dynamic visible: by quantifying the cascade barriers that the literature obscures, it provides a counter-narrative to algorithmic systems that would otherwise encode manufactured death as statistical normality.

### *The path forward*

If validated, the model suggests that drug approval alone is insufficient. Ending manufactured death for PWID requires:

1. **Regulatory action:** FDA approval for PWID indication
2. **Decriminalization:** Removing the dominant barrier (52·5% of attrition)
3. **Infrastructure:** SSP-integrated delivery leveraging existing touchpoints
4. **Continuity:** In-custody PrEP access preventing incarceration-related interruption

These are policy choices, not scientific limitations. The model suggests that pharmacology has solved the prevention problem. Policy has not.

## Conclusion

Computational modeling suggests that current US policy creates conditions meeting the operational definition of manufactured death for PWID: systematic foreclosure of biomedical prevention pathways regardless of drug efficacy. The model estimated cascade completion at 0·04% for PWID versus 53% for MSM using identical pharmacology—a 1,325-fold disparity attributable entirely to policy architecture.

For 44 years, PWID have been excluded from HIV prevention trials, denied regulatory approval, and subjected to criminalization that the model identifies as the dominant cascade barrier. The result is a population for whom effective prevention exists but cannot be accessed.

The term "manufactured death" names this condition with precision. The deaths are manufactured because the barriers are manufactured—constructed through policy decisions that can be reversed. The 85,000 additional individuals who could achieve protection under comprehensive harm reduction represent the policy gap: not epidemic inevitability, but policy choice.

These estimates require prospective validation. But the underlying pattern—44 years of exclusion producing cascade completion approaching zero—is not a model output. It is documented history.

## 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. This manuscript was developed independently.

**Data sharing:** Code available at [repository]. Supplementary File S1 provides AI Readiness assessment.

**Funding:** None.

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