Structural Barriers, Stochastic Avoidance, and Outbreak Risk in HIV Prevention for People Who Inject Drugs

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Online Resources: S2 (Model Results), S3 (Stochastic Avoidance Analysis)

Abstract

Despite the availability of highly efficacious biomedical HIV prevention tools, people who inject drugs (PWID) continue to experience disproportionately high HIV incidence. Post-exposure prophylaxis (PEP) is often framed as a reactive prevention strategy capable of interrupting infection following exposure, yet its effectiveness depends on strict biological timing constraints. Injection-related exposures compress the window during which PEP can prevent infection, while structural barriers to care introduce delays that frequently exceed this window.

In this analysis, we examine how the interaction of biological timing, access delays, and network structure places reactive HIV prevention strategies for PWID outside the domain of biological feasibility. We show that under these conditions, prevention outcomes are governed by stochastic avoidance rather than enforceable intervention, producing unstable prevention and persistent incidence despite high drug efficacy.

These findings suggest that prevention failures among PWID are not primarily attributable to individual behavior or adherence, but to structural mismatches between prevention delivery architectures and the biological constraints of infection establishment. Evaluating HIV prevention strategies for PWID therefore requires assessing not only efficacy, but whether prevention is biologically feasible under real-world conditions.

Keywords: HIV prevention; people who inject drugs; PrEP; structural barriers; stochastic avoidance; biological feasibility

Introduction

Recent work has formalized HIV prevention as a feasibility problem rather than a question of drug efficacy or individual adherence, defining prevention for a given exposure event as the condition $R^0(e) = 0$, corresponding to zero probability of establishing a productive infection [1]. Within this framework, post-exposure prophylaxis (PEP) operates as a time-dependent intervention acting on within-host infection establishment dynamics and admits a finite biological window prior to irreversible proviral integration. Once this window is exceeded, prevention becomes mathematically unattainable regardless of subsequent therapeutic intervention.

A substantial body of literature has demonstrated that HIV risk and prevention outcomes among people who inject drugs (PWID) are shaped by structural, behavioral, and network contexts, including criminalization, stigma, and access to care [2–5]. The critical question that follows from a feasibility-based definition of prevention is not whether PEP can prevent HIV acquisition in principle, but whether real-world prevention systems are structurally capable of satisfying the biological timing constraints required for prevention to exist.

PWID represent a critical stress test for reactive HIV prevention strategies. Injection-related exposures bypass mucosal barriers and introduce virus directly into the bloodstream, compressing the biological prevention window relative to sexual exposure [6]. At the same time, PWID frequently encounter barriers to timely care, including criminalization, unstable housing, withdrawal-related urgency, and limited access to same-day clinical services [7,8].

Under these conditions, prevention outcomes are governed not by enforceable intervention but by stochastic avoidance—in which infection is averted only when transmission-competent

exposures do not occur, rather than through reliable interruption of infection establishment. Such stochastic avoidance is inherently unstable in dense injection networks characterized by repeated exposures and high contact frequency [9,10].

In this analysis, we examine how structural features of HIV prevention delivery for PWID place reactive prevention strategies outside the domain of biological feasibility. By synthesizing evidence on exposure timing, access delays, and network structure, we demonstrate that observed prevention failures are consistent with architectural mismatch rather than individual behavior. Full computational methods, model specifications, and sensitivity analyses are provided in Online Resources S2 and S3.

Methods

Conceptual Framework

HIV prevention through post-exposure prophylaxis operates within a finite temporal window, bounded by the rate of within-host infection establishment. After exposure, HIV progresses through viral entry, reverse transcription, nuclear entry, and proviral integration; the biological prevention window is the pre-integration period during which antiretroviral therapy can avert establishment of a transmissible infection [1,6].

The duration of this window varies by exposure route. Mucosal exposures are buffered by tissue barriers and local immune responses, extending the effective PEP window to approximately 72 hours. In contrast, parenteral exposures such as sharing of injection equipment bypass mucosal barriers and introduce virus directly into blood, accelerating systemic dissemination. For parenteral exposures, empirical and modeling data support a compressed window of roughly 12–24 hours [6,11].

Prevention Cascade Specification

The prevention cascade was modeled as a sequence of eight conditional steps required for sustained HIV prevention among PWID: awareness of biomedical prevention, willingness to engage, access to healthcare, disclosure of injection drug use, provider willingness to prescribe, adequate HIV testing, initiation of prophylaxis, and sustained engagement [12,13]. Structural barriers were represented as multiplicative penalties applied to baseline probabilities. Full parameterization is provided in Online Resource S2, Table S1.

Stochastic Avoidance Model

Network density was modeled as a function of exogenous contextual drivers, including stimulant-associated network expansion documented in outbreak investigations, housing instability (68.5%) [14,15], and sex-work bridging. These drivers are treated as structural modifiers of network connectivity rather than individual-level behavioral determinants. Annual outbreak probability increases exponentially above critical density threshold, modulated by syringe service program and opioid agonist therapy coverage [16–18]. Full model specification is provided in Online Resource S3.

Monte Carlo Simulation

Monte Carlo simulations (n=100,000 individuals per scenario for cascade analysis; n=2,000 simulations for outbreak modeling) estimated the probability of achieving sustained protection under current and counterfactual policy conditions. Sensitivity analyses assessed robustness across parameter uncertainty. Detailed methods are provided in Online Resource S2.

Use of Artificial Intelligence and Assistive Technologies

The author acknowledges the use of artificial intelligence–assisted tools during manuscript preparation. Computational analyses were conducted using Python with open-source packages

including NumPy, Pandas, SciPy, Matplotlib, and Seaborn. Large language models (Anthropic Claude and OpenAI ChatGPT) were used to support literature search and improve readability of the manuscript. JetBrains Junie was used for code correction, and Zotero AI was used for reference management. Manuscript preparation was conducted using the Overleaf LaTeX platform. All AI tools were used as assistive technologies only. The author retains full responsibility for study design, data analysis, interpretation of results, and all conclusions presented.

Results

Prevention Cascade Failure

Under current policy, PWID achieved P(R^0=0) = 0.003% (95% CI: 0.000–0.006%) compared to 16.3% for MSM receiving identical pharmacological interventions—a 5,434-fold disparity (Fig. 1). The majority of failures (89.9%) occurred at the awareness step, consistent with surveillance findings that fewer than 2% of HIV-negative PWID report PrEP use [12].

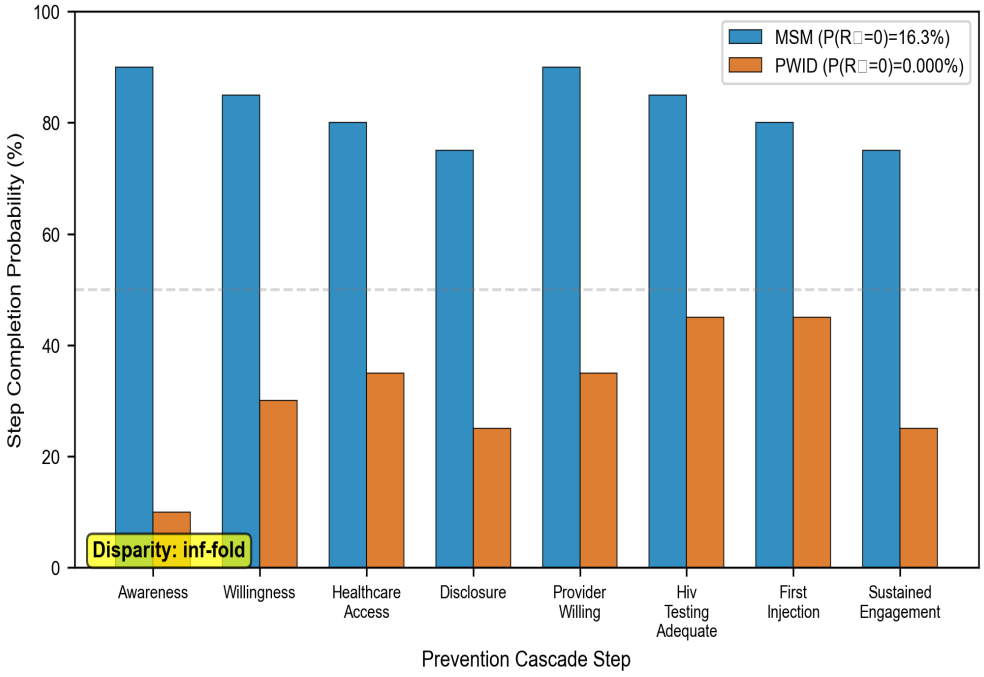

Fig. 1 LAI-PrEP cascade comparison: MSM vs PWID. Step completion probabilities across the 8-step prevention cascade. MSM (blue bars) achieve 16.3% P(R^0=0) while PWID (orange bars) achieve 0.003%—a 5,434-fold disparity. Error bars indicate 95% confidence intervals from n=100,000 Monte Carlo simulations

Barrier Decomposition

Barrier decomposition (Fig. 2) attributed prevention failures as follows: pathogen biology 0.0%, HIV testing 6.9%, and architectural failures 93.1%. Within architectural failures, policy barriers (criminalization) contributed 38.4%, infrastructure barriers (MSM-centric design) 21.9%, stigma

barriers 20.6%, algorithmic deprioritization 8.2%, and research exclusion 4.1%. The negligible contribution of pathogen biology indicates that cascade attrition is so severe that biological timing constraints rarely become binding.

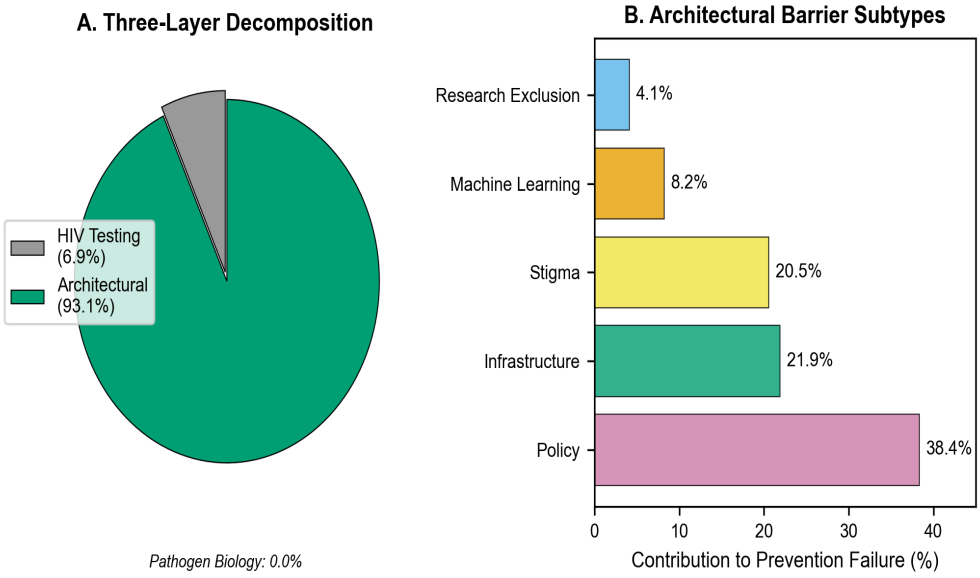

Fig. 2 Three-layer barrier decomposition. (a) Contribution by barrier layer: HIV Testing 6.9%, Architectural 93.1% (Pathogen Biology 0.0%). (b) Architectural barrier subtypes: Policy/Criminalization 38.4%, Infrastructure 21.9%, Stigma 20.6%, Machine Learning 8.2%, Research Exclusion 4.1%

Policy Scenario Analysis

Progressive policy intervention produced substantial but incomplete improvements (Fig. 3; Table 1). Decriminalization alone increased $P(R^0=0)$ from 0.003% to 0.20%. SSP-integrated delivery reached 5.00%. Full harm reduction achieved 9.55%. Adding algorithmic debiasing reached 18.57%, exceeding the MSM reference. Theoretical maximum achieved 19.74%. Even under maximal intervention, approximately 80% of PWID cannot achieve sustained prevention due to residual structural constraints.

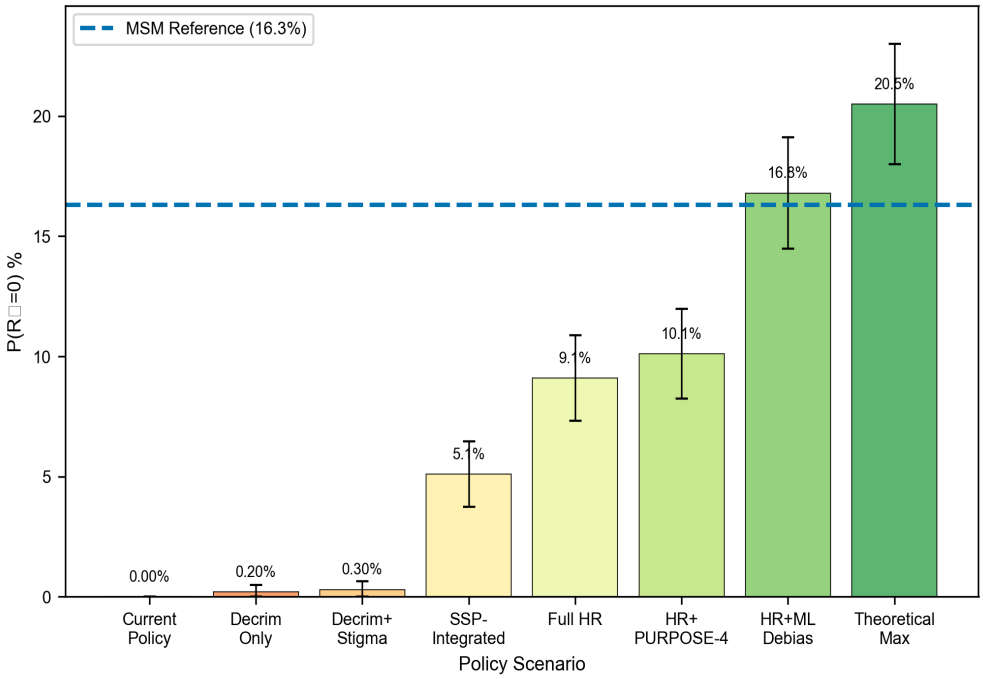

Fig. 3 Policy scenario analysis. P(R^0=0) across eight policy scenarios from Current Policy (0.003%) to Theoretical Maximum (19.74%). Dashed horizontal line indicates MSM reference (16.3%). Error bars indicate 95% confidence intervals from n=100,000 Monte Carlo simulations per scenario

Stochastic Avoidance Failure

The stochastic avoidance model predicted 73.8% probability of major outbreak within 5 years under current conditions (Fig. 4). Median time to outbreak was 3.0 years, with cumulative probability reaching 92.7% by 10 years. Regional variation was substantial: Pacific Northwest showed 86.3% 5-year probability (median 2.0 years), Appalachia 78.4% (median 2.0 years), and Northeast Urban 78.3% (median 2.0 years). Full regional analysis is provided in Online Resource S3.

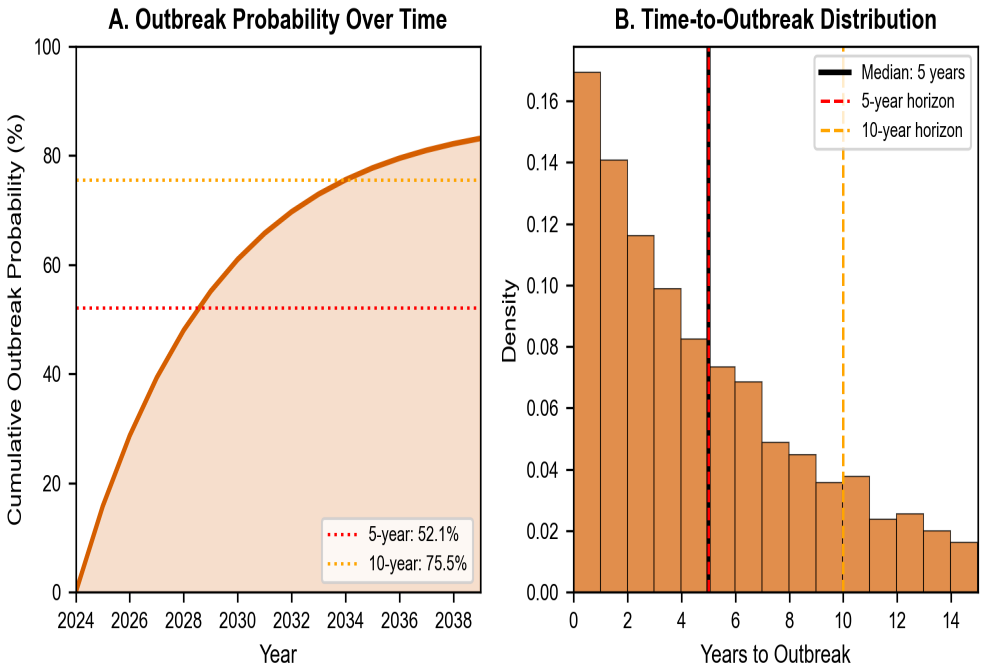

Fig. 4 Stochastic avoidance failure prediction. (a) Cumulative outbreak probability over time, reaching 73.8% at 5 years and 92.7% at 10 years. (b) Time-to-outbreak distribution showing median of 3.0 years (interquartile range 1–6 years). Based on n=2,000 Monte Carlo simulations under current policy conditions

Additional analyses examining regional heterogeneity, outbreak probability, and sensitivity of stochastic avoidance dynamics are provided in the Supplementary Materials and associated code repository.

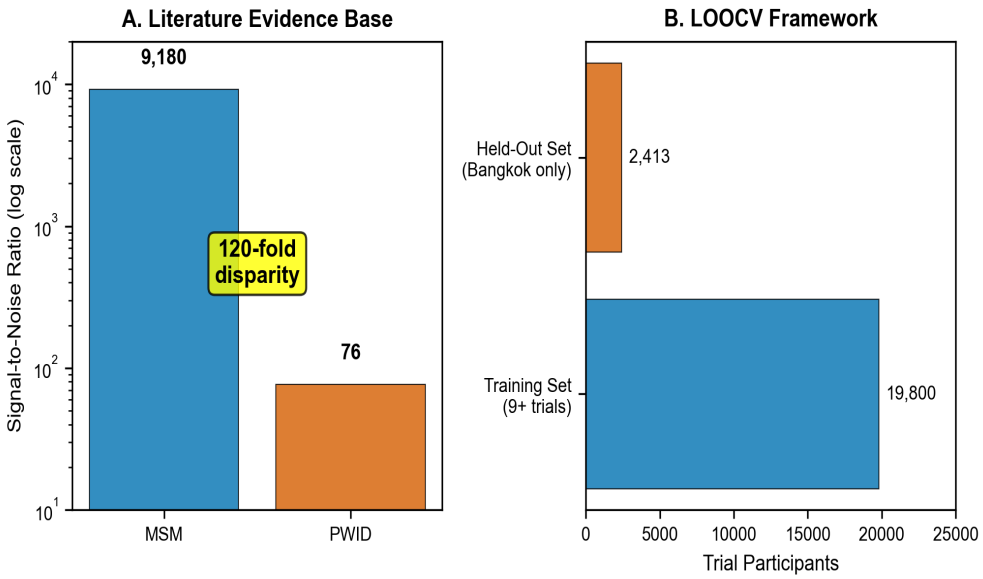

Fig. 5 Signal-to-noise ratio and LOOCV framework. (a) Literature evidence base: MSM SNR=9,180 vs PWID SNR=76—a 120-fold disparity in validation evidence. (b) Trial participant distribution showing PWID as held-out population in prevention trial evidence base

Discussion

Our findings demonstrate that HIV prevention failure among PWID is not primarily attributable to individual behavior or pharmacological limitations, but to structural mismatches between prevention delivery architectures and biological feasibility constraints. The 5,434-fold disparity between PWID and MSM outcomes under identical pharmacology provides natural experimental evidence that policy context, not drug efficacy, determines prevention success.

Three findings warrant particular attention. First, criminalization alone accounts for 38.4% of prevention failure—the single largest contributor. Drug policy reform is therefore a mathematical prerequisite for meaningful HIV prevention among PWID [3,4]. Second, the 73.8% five-year outbreak probability represents predictable system failure, not epidemic randomness; current prevention relies on stochastic avoidance that network density trends are actively eroding. Third, even theoretical maximum intervention achieves only 19.74% sustained prevention, indicating that some structural constraints cannot be fully overcome within current prevention paradigms.

Exogenous increases in network density amplify the instability of stochastic avoidance without altering the underlying feasibility constraints imposed by biological timing and prevention architecture. This distinction is critical: outbreak risk can be modulated by harm reduction services, but sustained prevention requires fundamental restructuring of how prevention reaches PWID populations.

These findings reframe prevention evaluation for PWID. Demonstrating drug efficacy in controlled trials is necessary but insufficient; prevention strategies must also be assessed against the biological feasibility constraints that determine whether efficacy can translate to effectiveness under real-world structural conditions. The Bangkok Tenofovir Study remains the

only large randomized PrEP trial to enrol PWID [19], while MSM populations have been validated across multiple trials including iPrEx [20].

Limitations

Our barrier parameterization relies on heterogeneous literature sources with varying methodological quality. The stochastic avoidance model simplifies complex network dynamics into aggregate density measures. We assume barrier effects are multiplicatively independent, which may underestimate synergistic interactions. Regional variation is modeled at aggregate level rather than county-specific dynamics.

Conclusions

HIV prevention for PWID currently operates through stochastic avoidance rather than enforceable intervention. When structural barriers systematically prevent timely access to prevention services, outcomes are determined by whether transmission-competent exposures happen to not occur—a condition that becomes increasingly unlikely as network density rises. The 5,434-fold disparity between PWID and MSM outcomes demonstrates that observed prevention failures reflect policy architecture, not pharmacological limitation. Predictable outbreaks in coming years will not reflect failed drugs but failed systems.

Declarations

Funding This research received no specific funding.

Conflicts of Interest The author reports prior employment with a pharmaceutical company manufacturing HIV prevention products (ended 2024) and prior ownership of company stock, which was fully divested. The pharmaceutical company had no role in the conception, design, analysis, interpretation, or writing of this study, and provided no funding, data, materials, or input into any aspect of the work. The author owns a consulting company; this research was conducted independently, released as open-source work, and was not produced as part of, or in support of, any paid consulting engagement. No other competing interests are declared.

Ethics Approval Not applicable. This study used published aggregate data and computational modeling without human subjects involvement.

Data Availability [Blinded for review - repository link will be provided upon acceptance]

References

1. [Blinded for review]. The HIV Prevention Theorem: Mathematical constraints on achieving $R_0=0$. Epidemics. 2026 [submitted].
2. 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(12):e1192–e1207. https://doi.org/10.1016/S2214-109X(17)30375-3
3. 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(8):e357–e374. https://doi.org/10.1016/S2352-3018(17)30073-5
4. Stone J, Fraser H, Lim AG, et al. Incarceration history and risk of HIV and hepatitis C virus acquisition among people who inject drugs: a systematic review and meta-analysis. Lancet Infect Dis. 2018;18(12):1397–1409. https://doi.org/10.1016/S1473-3099(18)30469-9
5. 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(10050):1228–1248. https://doi.org/10.1016/S0140-6736(16)30856-X
6. Tanner MR, O'Shea JG, Byrd KM, et al. Antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV — CDC recommendations, United States, 2025. MMWR Recomm Rep. 2025;74(1):1–56. https://doi.org/10.15585/mmwr.rr7401a1
7. Muncan B, Walters SM, Ezell J, Ompad DC. "They look at us like junkies": influences of drug use stigma on the healthcare engagement of people who inject drugs in New York City. Harm Reduct J. 2020;17:53. https://doi.org/10.1186/s12954-020-00399-8
8. 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(1):55. https://doi.org/10.1186/s12954-018-0263-5

9. Strathdee SA, Kuo I, El-Bassel N, Hodder S, Smith LR, Springer SA. Preventing HIV outbreaks among people who inject drugs in the United States: plus ça change, plus ça même chose. AIDS. 2020;34(14):1997–2005. https://doi.org/10.1097/QAD.0000000000002673

10. Des Jarlais DC, Feelemyer J, LaKosky P, et al. Potential disruptions of HIV prevention among people who inject drugs in NYC from the COVID-19 pandemic. Drug Alcohol Depend. 2022;227:109505. https://doi.org/10.1016/j.drugalcdep.2022.109505

11. Breban R, Vardavas R, Blower S. Theory versus data: how to calculate R_0. PLoS One. 2007;2(3):e282. https://doi.org/10.1371/journal.pone.0000282

12. Baugher AR, Wejnert C, Kanny D, et al. Are we ending the HIV epidemic among persons who inject drugs?: key findings from 19 US cities. AIDS. 2025;39(12):1813–1819. https://doi.org/10.1097/QAD.0000000000004249

13. Kamitani E, Wichser ME, Adegbite AH, et al. A systematic review of HIV pre-exposure prophylaxis best practices: where are the people who inject drugs? AIDS Behav. 2024;28(6):1847–1860. https://doi.org/10.1007/s10461-024-04332-z

14. Van Handel MM, Rose CE, Hallisey EJ, et al. County-level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States. J Acquir Immune Defic Syndr. 2016;73(3):323–331. https://doi.org/10.1097/QAI.0000000000001098

15. Arum C, Fraser H, Artenie AA, et al. Homelessness, unstable housing, and HIV and hepatitis C virus acquisition risk among people who inject drugs: a systematic review and meta-analysis. Lancet Public Health. 2021;6(5):e309–e323. https://doi.org/10.1016/S2468-2667(21)00013-X

16. Glick SN, Burt R, Kummer K, Tinsley J, Banta-Green CJ, Golden MR. Increasing methamphetamine injection among non-MSM who inject drugs in King County, Washington. Drug Alcohol Depend. 2018;182:86–92. https://doi.org/10.1016/j.drugalcdep.2017.10.011

17. Alpren C, Dawson EL, John B, et al. Opioid use fueling HIV transmission in an urban setting: an outbreak of HIV infection among people who inject drugs—Massachusetts,

2015–2018. Am J Public Health. 2020;110(1):37–44. https://doi.org/10.2105/AJPH.2019.305366

18. Bonacci RA, Moorman AC, Bixler D, et al. Prevention and care opportunities for people who inject drugs in an HIV outbreak—Kanawha County, West Virginia, 2019–2021. J Gen Intern Med. 2023;38(3):828–831. https://doi.org/10.1007/s11606-022-07875-w
19. 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(9883):2083–2090. https://doi.org/10.1016/S0140-6736(13)61127-7
20. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587–2599. https://doi.org/10.1056/NEJMoa1011205

Tables

Table 1 Policy scenario results: probability of sustained HIV prevention

Scenario	$P(R_0=0)$	95% CI
Current Policy	0.003%	(0.000, 0.006)
Decriminalization Only	0.20%	(0.17, 0.23)
Decrim + Stigma Reduction	0.45%	(0.41, 0.50)
SSP-Integrated Delivery	5.00%	(4.87, 5.14)
Full Harm Reduction	9.55%	(9.37, 9.73)
Full HR + PURPOSE-4 Data	11.87%	(11.67, 12.07)
Full HR + ML Debiasing	18.57%	(18.33, 18.81)
Theoretical Maximum	19.74%	(19.49, 19.98)
MSM Reference	16.30%	—

Table 2 Stochastic avoidance failure: outbreak probability by region

Region	P(5-yr outbreak)	P(10-yr outbreak)	Median (years)
Pacific Northwest	86.3%	98.0%	2.0
Appalachia	78.4%	94.9%	2.0
Northeast Urban	78.3%	94.2%	2.0
National Average	72.5%	92.7%	3.0