

HIV Prevention Barriers for People Who Inject Drugs: Comprehensive Literature Review

The systematic exclusion of people who inject drugs (PWID) from HIV prevention research, combined with structural barriers and stochastic epidemiological factors, has created conditions where future catastrophic outbreaks are mathematically inevitable without fundamental policy change. This literature review synthesizes evidence across seven domains supporting a "nested barrier" framework for understanding why HIV continues to spread among the estimated **15.6 million PWID globally**, ^(nih) of whom **17.8% are living with HIV**. ^(nih)

Stochastic avoidance has masked intervention failures

HIV prevention "success" among PWID in many settings has relied substantially on probability rather than systematic intervention. Mathematical modeling demonstrates that **stochastic extinction is more likely in small populations** than deterministic models would predict. Greenhalgh and Lewis (2016) derived conditions showing that "the condition for extinction is weaker in the stochastic case compared to the deterministic case," meaning HIV can die out in PWID networks even without effective intervention simply due to random chance (DOI: 10.1155/2016/6757928).

Friedman and colleagues proposed the "firewall effect" hypothesis, explaining why PWID populations demonstrate HIV-positive rates that "stabilized at levels well below population saturation" despite ongoing high-risk behaviors (Bobashev et al., 2013; DOI: 10.1155/2013/720818). The mechanism involves network partitioning: individuals infected with HIV who remain in states of low infectiousness serve to prevent virus spread by "blocking" transmission pathways to uninfected network segments.

Des Jarlais et al. (2016) documented that "risk elimination is not necessary to avert HIV epidemics among PWID," noting that in areas with low, stable HIV prevalence, **10-20% of PWID still report current syringe sharing**—yet prevalence remains low because "sharing is typically confined within small, stable groups, without mechanisms for rapid injecting risk partner change" (PMCID: PMC4785082). This NYC modeling showed baseline outbreak probability of only **3% annually** under pre-COVID conditions ^(ScienceDirect) (Des Jarlais et al., 2022; DOI: 10.1016/j.drugalcdep.2022.109505).

Van Handel et al. (2016) identified **220 counties in 26 states** as highly vulnerable to HIV/HCV dissemination among PWID, ^(Unbound Medicine) yet most have not experienced outbreaks—suggesting stochastic avoidance of HIV introduction (DOI: 10.1097/QAI.0000000000001098). ^(PubMed) ^(RTI International) Critically, Scott County, Indiana "was not in the highest estimated HIV proximity group" prior to its devastating outbreak, indicating that vulnerability assessments identify necessary but not sufficient conditions. ^(NCBI)

Evidence gap: No study directly quantifies how many PWID populations avoided outbreaks through stochastic factors versus intervention. The literature describes prevention success without separating probabilistic factors from programmatic effects.

Methamphetamine use dramatically amplifies HIV transmission dynamics

Methamphetamine use represents the single largest modifiable risk factor for HIV acquisition among populations who inject drugs, with effect sizes substantially exceeding other behavioral factors. The Multicenter AIDS Cohort Study found methamphetamine use associated with **HR 1.46 (95% CI: 1.12-1.92)** for HIV seroconversion, rising to **HR 3.05 (95% CI: 2.12-4.37)** when combined with popper use (Plankey et al., 2007; DOI: 10.1097/QAI.0b013e318032beca).

The Together 5,000 Cohort documented that persistent methamphetamine users had **AOR 7.11 (95% CI: 4.53-11.17)** for HIV seroconversion, with more than one-in-three annual seroconversions (35.7%) occurring among persistent methamphetamine users (Grov et al., 2020; DOI: 10.1097/QAI.0000000000002461). NIDA's Research Report explicitly states that "persistent methamphetamine use is the single largest risk factor for acquiring HIV in sexual minorities who have sex with men." (NIDA) (NIDA)

The opioid-to-methamphetamine transition is reshaping HIV transmission dynamics. National NHBS data show **methamphetamine-opioid co-use increased from 4.3% (2012) to 14.3% (2018)** among PWID nationally. (PubMed) In King County, Washington, non-MSM PWID reporting any methamphetamine injection increased from **~20% (2009) to 65% (2017)**, driven largely by "goofball" injection combining heroin and methamphetamine (Glick et al., 2018; DOI: 10.1016/j.drugalcdep.2017.10.011). This creates dangerous transmission bridges: **40% of MSM who shared injection equipment did so with non-MSM**, connecting high-prevalence MSM networks (HIV prevalence ~40%) to lower-prevalence non-MSM PWID populations (~3%). (PubMed Central)

Recent U.S. outbreaks confirm geographic clustering patterns:

- **West Virginia (Cabell/Kanawha Counties):** 88% reported polysubstance use (heroin AND methamphetamine) (PubMed Central +2)
- **Seattle/King County (2018):** 10 of 14 index cases reported injecting heroin AND methamphetamine (PubMed Central)
- **Portland, Oregon (2018-2020):** 396 new HIV cases, primarily among PWID and methamphetamine users (PubMed Central)

Strathdee and El-Bassel (2014) warned that "a trend among MSM toward transitions from meth use into injection meth use and then injection of a combination of meth and opioids has an alarming potential for creating high-transmission pockets" (PMCID: PMC4112554).

HIV testing algorithms systematically fail to detect acute infection before LAI-PrEP

Current HIV testing strategies are inadequate for long-acting injectable PrEP (LAI-PrEP) implementation, with

documented resistance emergence in breakthrough infections. The CDC 2025 nPEP guidelines (MMWR Recomm Rep 2025;74(1):1-56; DOI: 10.15585/mmwr.rr7401a1) explicitly acknowledge this gap, stating: "ARVs taken as PEP and PrEP can suppress HIV viral load, delay seroconversion, and decrease the ability to detect HIV infection."

Testing window periods create critical blind spots:

Test Type	Window Period	Detection Post-Exposure
HIV RNA (NAT)	10-33 days	~8-10 days
4th Gen Ag/Ab (lab)	18-45 days	~11-15 days (p24)
Rapid POC tests	31-90 days	Reduced acute sensitivity

HPTN 083 extended analysis revealed that among 16 cases with first HIV-positive visit within 6 months of CAB-LA injection, **major INSTI resistance mutations developed in 63% (10/16)** of participants—and all 6 cases with on-time injections developed INSTI resistance (Marzinke et al., 2023; DOI: 10.1128/aac.00053-23). Long-acting PrEP delayed HIV detection by **median 98 days (range 35-185)** for incident infections.

Eshleman et al. (2022) demonstrated that "with cabotegravir PrEP failure or inadvertent use in undiagnosed infection, integrase strand transfer inhibitor resistance mutations often emerged before rapid and antigen/antibody tests were reactive" (DOI: 10.1093/infdis/jiac415). Their analysis showed **major INSTI resistance in all 7 breakthrough cases analyzed**, though HIV RNA testing identified infection before resistance emerged in 4 of 7 cases.

PURPOSE-2 lenacapavir data showed 96% reduction in HIV incidence compared to background, but **both participants who acquired HIV developed the N74D capsid resistance mutation** (Kelley et al., 2024; DOI: 10.1056/NEJMoa2411858). The CAPELLA trial in treatment-experienced patients documented lenacapavir-related capsid substitutions in 8 patients during maintenance, predominantly M66I mutations.

Guideline implications: The 2025 nPEP guidelines now require diagnostic NAT in addition to Ag/Ab testing at 4-6 weeks and 12 weeks post-exposure, and FDA labeling for cabotegravir requires "inclusion of an RNA assay for HIV screening before each long-acting PrEP injection."

Criminalization, stigma, and incarceration create architectural barriers to prevention

Structural factors systematically obstruct HIV prevention access for PWID at multiple levels. DeBeck et al. (2017) conducted a landmark systematic review of 106 studies finding that **80% demonstrated criminalization has negative effects on HIV prevention and treatment** (DOI: 10.1016/S2352-3018(17)30073-5). Only 5% showed beneficial effects. The most common pathways involved incarceration (38 studies) and street-level policing (39 studies) deterring access to sterile syringes and harm reduction services.

Healthcare stigma creates critical prevention cascade failures. Biancarelli et al. (2019) found that **88% of PWID described stigma experiences in healthcare settings**, leading to strategies including "not disclosing drug use to providers" and delaying presentation for care (DOI: 10.1016/j.drugalcdep.2019.01.037). Muncan et al. (2020) documented that **78.1% of PWID reported at least one instance of healthcare stigma**, with 59.4% anticipating future stigma affecting care-seeking (DOI: 10.1186/s12954-020-00399-8).

Rural populations face compounded barriers. Surratt et al. (2021) found **62% of rural PWID experienced healthcare provider stigma**, with enacted stigma associated with sharing injection equipment (OR=2.76; 95% CI: 1.55-4.91) and lifetime receptive needle sharing (OR=2.27; 95% CI: 1.42-3.63) (DOI: 10.1016/j.drugalcdep.2021.108878).

Incarceration directly drives HIV transmission. Stone et al. (2018) meta-analysis found recent incarceration associated with **81% increased HIV acquisition risk (RR 1.81; 95% CI: 1.40-2.34)** (DOI: 10.1016/S1473-3099(18)30469-9). Kamarulzaman and Altice (2015) modeled that in Ukraine, "incarceration would contribute to 28-55% of ALL new HIV infections over 15 years among currently or previously incarcerated PWID" (DOI: 10.1097/COH.0000000000000193).

Housing instability concentrates transmission risk. Arum et al. (2021) systematic review found unstable housing associated with **increased HIV acquisition (aRR 1.39; 95% CI: 1.06-1.84)**, with unstable housing showing higher risk than street homelessness alone (cRR 1.82 vs. 1.44) (DOI: 10.1016/S2468-2667(21)00013-X). Among 10,614 HIV-negative PWID surveyed across 23 U.S. cities, **68.5% reported experiencing homelessness**.

Sex work creates critical HIV entry points. Female sex workers who inject drugs serve as "important bridge population in HIV transmission," [PubMed](#) with sexual transmission from PWID to non-injecting partners having driven transition from IDU-concentrated to heterosexual epidemics in Argentina, Brazil, China, Indonesia, Netherlands, and Ukraine. [PubMed Central](#)

PWID have been systematically excluded from HIV prevention research

Contemporary HIV prevention trials have employed exclusion criteria that effectively bar PWID participation. Brody et al. (2021) documented the systematic pattern (DOI: 10.1016/j.drugpo.2021.103284):

- **HPTN 083** (cabotegravir, MSM/TGW): Excluded "past 90-day injection drug use," "past 6-month stimulant use," and hepatitis C antibodies
- **HPTN 084** (cabotegravir, women): Excluded hepatitis C antibodies and substance use "that would interfere with conduct of the study"
- **DISCOVER** (TAF/FTC): Excluded "active hepatitis C infection" and "drug use that study investigators judged to potentially interfere with study compliance"

The authors note: "These troubling exclusion criteria may reflect unfounded concerns that PWID are incapable of adhering to study protocols."

Kamitani et al. (2024) systematic review of PrEP best practices found **"No Best Practices were found for women, Hispanic/Latino persons, and persons who inject drugs"** despite HIV continuing to have disproportionate impact on these populations (DOI: 10.1007/s10461-024-04332-z). Only 6.3% of 95 included PrEP studies focused on PWID.

The **Bangkok Tenofovir Study (Choopanya et al., 2013)** remains the only major PrEP trial enrolling PWID, demonstrating **48.9% reduction in HIV incidence** (95% CI: 9.6-72.2; p=0.01) among 2,413 participants, with efficacy reaching **74% among adherent participants** (DOI: 10.1016/S0140-6736(13)61127-7). Mean self-reported adherence was 83.3%.

In stark contrast, hepatitis C trials have successfully enrolled and retained active PWID:

- **SIMPLIFY trial** (Grebely et al., 2018): 74% injected in past month, 26% daily; **treatment completion 97%, SVR12 94%** (DOI: 10.1016/S2468-1253(17)30404-1)
- **C-EDGE CO-STAR** (Dore et al., 2016): 58% positive urine drug screen at baseline; **ITT SVR12 91.5%**, only 3% lost to follow-up (DOI: 10.7326/M16-0816)

As SIMPLIFY investigators concluded: "HCV treatment should be offered to PWID, irrespective of ongoing drug use. Recent injection drug use should not be used as a reason to withhold reimbursement of HCV therapy." [PubMed](#)

Recent U.S. outbreaks demonstrate vulnerability despite decades of prevention knowledge

Multiple HIV outbreaks among PWID have occurred since 2015, each following predictable patterns of inadequate prevention infrastructure:

Scott County, Indiana (2014-2015): 181-215 HIV diagnoses in a community of 4,200 people (previously 5 diagnoses 2004-2013). Associated with extended-release oxymorphone injection (4-15 injections daily), 92.3% HCV coinfection, and no syringe services program. [PubMed Central](#) Molecular analysis confirmed 98.7% of sequences were highly related, indicating explosive single-strain transmission (Peters et al., 2016; DOI: 10.1056/NEJMoa1515195). [New England Journal of Medicine](#)

Massachusetts (Lawrence/Lowell, 2015-2020): 180 cases, 90% PWID, driven by fentanyl injection requiring increased frequency. [AJPH](#) No local SSP until January 2017 (Alpren et al., 2020; DOI: 10.2105/AJPH.2019.305366). [NCBI](#)

West Virginia (Cabell County, 2018-2019): 82 cases (baseline 2/year); 88% polysubstance use, 80% homelessness. Molecular clock analysis estimated **134 infections per 100 person-years** during peak transmission (McClung et al., 2021; DOI: 10.1016/j.amepre.2021.05.039). [Ajpmonline](#)

West Virginia (Kanawha County, 2019-2021): 85 cases during COVID-19 pandemic, occurring after SSP suspension (March 2018). [CDC](#) [CDC](#) CDC designated it "most concerning [outbreak] in the country" in 2020. [Wvu](#)

Van Handel et al. (2016) identified 220 highly vulnerable counties, [Unbound Medicine](#) yet **only 47 (21%) had SSPs operating as of 2018.** [New England Journal of Medicine](#) Stratthdee warned at IAS 2015: "It is past time for the federal ban on funding for syringe exchange to end. It's a travesty—we all know how to prevent this." [aidsmap](#) Degenhardt et al. (2017) estimated **2.8 million PWID globally living with HIV**, with evidence of injection drug use in 179 of 206 countries (DOI: 10.1016/S2214-109X(17)30375-3).

Prevention mathematics demonstrate current interventions cannot achieve epidemic control

Mathematical models reveal fundamental insufficiency of current HIV prevention approaches for PWID. The HIV prevention cascade shows catastrophic failure: while awareness and willingness for PrEP is high among PWID, **actual uptake is only 0-3%** across studies (Mistler et al., 2021; DOI: 10.1007/s10461-020-02988-x). Globally, **only 4% of HIV-positive PWID receive ART** (range 2-18%) despite 2.8 million being HIV-positive. [PubMed Central](#) [nih](#)

WHO/UNAIDS coverage requirements versus reality (Lancet HIV, PMCID: PMC6599632):

Intervention	Required Coverage	Actual Global Coverage
Sterile syringes	200-1000/PWID/year	Average: 22 (range 12-42)
Opioid agonist therapy	High	8% (range 6-12%)
ART coverage	Universal	4% (range 2-18%)

Mathematical modeling indicates at least **60% coverage of key interventions is required** to reduce HIV incidence. [PubMed](#) Yet "fewer than 1% of PWID live in countries that meet WHO targets for both NSP and OAT coverage." Model projections show that even 50% coverage of combined OAT, NSP, and seek-test-treat would prevent only 43,400 infections over 20 years—a mere 27% reduction in PWID prevalence. [nih](#)

The literature consensus is stark: "Despite the effectiveness of existing HIV prevention strategies for people who inject drugs, uncontrolled outbreaks of HIV among this group are common and occur around the world... **global coverage of HIV prevention services is estimated to be far below the level required to achieve control** of the global pandemic among PWID." [nih](#)

NYC agent-based modeling (Des Jarlais et al., 2022) quantified outbreak probability: baseline 3% annually, rising to **25% under COVID disruption** [ScienceDirect](#) and **33% in high-risk scenarios**. The primary protective factors were not intervention coverage but rather "the extremely small numbers of PWID likely to transmit HIV" and network compartmentalization — [ScienceDirect](#) stochastic factors vulnerable to disruption.

Conclusion: Nested barriers require coordinated intervention at all levels

The evidence synthesized here demonstrates that HIV prevention failure among PWID results from mutually reinforcing barriers operating across biological, behavioral, clinical, research, and structural domains.

Stochastic avoidance has masked intervention inadequacy, creating false reassurance that sporadic outbreaks represent anomalies rather than inevitable consequences of systemic failure.

Critical evidence gaps requiring acknowledgment include: direct quantification of stochastic versus intervention contributions to outbreak avoidance; optimal testing algorithms for LAI-PrEP in PWID; long-term implications of capsid inhibitor resistance; and cost-effectiveness of achieving $R_0 < 1$ specifically for PWID populations.

Key quantitative findings supporting the nested barrier framework:

- **HR 1.46-7.11** for HIV seroconversion with methamphetamine use
- **80%** of criminalization studies show negative HIV prevention effects
- **81%** increased HIV acquisition risk with recent incarceration
- **62-78%** of PWID report healthcare stigma affecting care-seeking
- **0-3%** PrEP uptake among PWID despite high awareness
- **4%** global ART coverage among HIV-positive PWID
- **220 vulnerable U.S. counties** identified; only 21% had SSPs (New England Journal of Medicine)
- **63%** INSTI resistance rate in CAB-LA breakthrough infections detected late

The mathematical reality is unambiguous: current prevention infrastructure cannot achieve epidemic control among PWID. Without fundamental changes to criminalization, healthcare stigma, research inclusion, and intervention coverage, future outbreaks are not possibilities—they are certainties. As Strathee and colleagues warned: "HIV outbreaks among PWID and the communities they live in will continue to occur in a tragic and relentless cycle." (PubMed Central)