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Preventing HIV among People who Inject Drugs in the United States: Plus ça Change, Plus ça Même Chose

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Introduction

In 1997, a serious HIV outbreak among people who inject drugs (PWID) occurred in Vancouver, Canada, during which HIV incidence peaked at 18.6/100 person years[1]. The outbreak was unusual since Vancouver had the largest volume syringe services programme (SSP) in North America and HIV prevalence among PWID had previously remained low. A contributing factor to the outbreak was an influx of powder cocaine that led PWID to inject more frequently than those who injected heroin[2] which outpaced the number of available syringes at the city's single fixed-site SSP[3]. In response, Canada expanded mobile SSPs, HIV testing and medications for opioid use disorder (MOUD), implemented ART as prevention (TasP) across the province of British Columbia, and later implemented the first supervised injection facility (SIF) and heroin maintenance programmes in North America[3, 4]. Consequently, Vancouver's HIV incidence among PWID plummeted and has since remained low[3].

The US response to the Vancouver HIV outbreak was polar opposite. The paper that first described the outbreak, which was published by the first author as an AIDS *Fast Track* article[1], was entered into the US Congressional record with the opposite interpretation: that SSPs had failed. Data from Vancouver and Montreal were then used as a political weapon to uphold the Congressional ban on the use of US federal funds to support SSPs[5], which was not permanently overturned until December, 2015. While SIFs now exist in Canada, Western Europe and Australia and have consistently been shown to reduce the harms

associated with injection drug use[6], only a few ‘underground’ SIFs exist in the US and all are unsanctioned by the federal government[7].

The politicization of SSPs and the War on Drugs dogma that prevailed more than twenty years ago still undermines HIV prevention among PWID in the US to this day, with repeatedly disastrous consequences. This editorial review was written by all-female researchers in honor of International Women’s Day, and covers current trends in the epidemiology of HIV among PWID in the US, with a special focus on women who inject drugs as well as three recent HIV outbreaks among PWID. We also discuss prevention and treatment cascades for HIV and MOUD among PWID. Finally, we propose lessons for US counties and other nations that are vulnerable to future HIV outbreaks.

The US Opioid Crisis and the Changing Epidemiology of HIV among PWID

Over the last decade, North America has been in the throes of a major opioid epidemic, due initially in part to over-prescribing of prescription opiates, followed by increasing availability of cheap (black tar) heroin, synthetic opioids (predominantly fentanyl), and stimulants including methamphetamine[8]. For the last three years, annual overdose deaths in the US surpassed annual deaths due to HIV/AIDS at its peak.

While HIV risks associated with injection of heroin and methamphetamine are well documented, fentanyl injection carries additional risks. First, fentanyl has a shorter half-life than heroin, and is typically injected more frequently, placing PWID at greater risk of syringe sharing[9]. Second, when available as a powder,

PWID can prepare fentanyl without heat, which some researchers speculate can inactivate HIV and HCV.[10, 11]

Changes in drug trafficking patterns and use reflect the changing epidemiologic profile of HIV infection among PWID in the US, which historically affected communities who were older, urban and African American[12, 13]. More recently, the majority of US HIV infections among PWID have been reported among persons who are younger, rural or suburban and Caucasian. Although the overall proportion of reported HIV cases among PWID in the US declined from 2010 to 2016, that decline has stalled, especially among Caucasians[14]. The US Medical Monitoring Project also reported disturbing increases in distributive needle sharing and unprotected sex among HIV-positive PWID[15].

Women Who Inject Drugs and HIV Risk.

In 2017, women comprised 28% of newly reported HIV infections among PWID in the US[16]. A meta-analysis of 117 studies across 14 countries suggest a modest increase (18%) in HIV risk among women who inject drugs compared to men, but only in high prevalence (>20%) settings.[17] Compared to men, women who inject drugs have greater overlap between their sexual and injection social networks[18] and are often initiated into drug use by male partners who exert significant control over their injection and sexual practices.[19, 20] Gender inequality and power imbalances often relegate women to be 'second to the needle,' and undermine condom negotiation. This not only increases HIV risk, but refusal to do so places women at risk for physical and sexual violence.[21] Men who initiate women into drug use are more likely to

have been incarcerated, share used syringes, inject others, and obtain syringes from informal sources, all known risk factors for HIV.[18] A prospective cohort study in Baltimore found HIV incidence was more than double among women injectors who had a male sexual partner that also injected drugs.[22] Women who engage in sex work and use drugs also experience heightened HIV risk due to shared injection equipment, condomless sex with clients and intimate partners, exposure to sexual violence, and incarceration.[20, 21]

HIV Surveillance among PWID and Recent Outbreaks

Among 11,437 PWID surveyed in 23 US cities for the National HIV Behavioral Surveillance study in 2018, overall HIV prevalence was 6%[23]. However, only 55% of PWID met CDC guidelines for annual HIV testing and nearly one-third reported using a syringe after someone else had previously used it, which was more common among young PWID[23]. More than half of PWID reported obtaining syringes from a SSP; but variability between cities ranged from 1% to 93%[23]. This disparity is due in part to uneven access to SSPs in many US communities, despite strong evidence of their effectiveness in reducing HIV incidence. [24] Lack of access to sterile syringes has consistently been associated with HIV outbreaks among PWID, especially in rural or semi-urban communities, as described below.

Scott County Outbreak. In rural Scott County, Indiana, an opioid analgesic, oxymorphone, began to be liberally prescribed by local medical providers after it was approved by the FDA in 2006. When the manufacturer switched to a more tamper-resistant formulation in 2012 and policy reform began limiting its

prescription, many patients who had developed an opioid use disorder switched to injecting it. Many PWID –including high proportions of young women—then turned to injecting black-tar heroin which was more available and less expensive[25]. Since both SSPs and pharmacy syringe sales without a prescription were illegal in Indiana, multi-person syringe sharing was common. A moratorium on methadone expansion in the state also meant there were few medical providers offering MOUD, and several free HIV testing locations had been closed due to moral concerns that they also offered abortions. Despite reports of escalating HCV incidence in the region[26], few efforts were made to scale up HIV prevention[27].

In 2015, an astute physician in Scott County observed an unusual cluster of new HIV diagnoses within a short period of time and reported it to the local health department, who then notified the CDC. By that time, HIV had already spread through PWID networks and their sexual contacts[25] resulting in 203 HIV infections, and a community-level HIV prevalence of 5%. Although implementation of SSPs subsequently led to a decrease in syringe sharing[28], a modeling analysis concluded that if SSPs and MOUD had been implemented earlier, 90% of HIV infections in the county could have been prevented[28]. A recent modeling analysis showed that a proactive response to implementing SSPs could have blunted the HIV outbreak among PWID as well as their sexual partners[28].

Due to growing concerns that similar outbreaks could be brewing, Van Handel and colleagues used surveillance data to conduct an ecological analysis examining characteristics associated with the Scott County outbreak, which

they used to identify 220 US counties in 26 states that were deemed vulnerable to future outbreaks[29]. Of these counties, half are located in the Appalachian region, which is predominantly rural, socioeconomically disadvantaged, and, like Scott County, lacking in robust harm reduction services.

West Virginia Outbreaks. West Virginia (WV) is the only US state that is located entirely in Appalachia. Since 2013, WV ranks among the highest in terms of national rates of acute hepatitis B and C[30] and has seen a rise in endocarditis cases related to injection drug use[31, 32]. In 2018, WV had the highest age-adjusted drug overdose death rate in the US (51.5/100,000)[33]. Unfortunately, these well-known harbingers of HIV outbreaks went unheeded. In Huntington city and surrounding Cabell County in southwestern WV, 82 HIV cases were identified since 2018, where the region previously averaged two new HIV diagnoses annually. Of these 82 cases, 92% were among PWID, 92% were white, 40% were women, 29% exchanged sex for money or drugs, and 88% tested HCV-positive[34]. Of 50 individuals with available HIV genetic sequencing data, 92% had closely related infections suggestive of rapid transmission[35].

Although SSP were introduced in Cabell County in 2015, strict eligibility requirements limited its access. Effective SSPs are operating in Huntington, Morgantown, and Harpers Ferry/Martinsburg, but the SSP in Charleston (WV's capital located in Kanawha county) that served thousands of clients was closed by the city government in 2018. Subsequently, 24 cases of HIV among PWID in Kanawha County were reported[36]. Last year, a bill was introduced in the WV

state legislature to abolish SSPs. Although it did not pass, ongoing opposition to SSPs in the state continues.

Massachusetts Outbreaks. From 2015 to 2018, two HIV outbreaks occurred in Lawrence and Lowell, both rural communities in northeast Massachusetts[35]. Like the Scott County outbreak, the Lawrence outbreak was first identified by an astute physician. Similar to the aforementioned outbreaks, 43% of new HIV diagnoses in Lawrence and Lowell were among women. In Massachusetts, however, its outbreaks were closely associated with frequent fentanyl injection. Genetic sequencing revealed several HIV clusters reflecting multiple introductions of HIV[36] as opposed to a point source. Molecular links at <0.5% genetic distance also confirmed that most infections were recent. SSPs were introduced in both counties but not until the outbreaks were well underway[37].

Continuum of Care Considerations: HIV Treatment, PrEP, and MOUD

A critical component in an HIV outbreak response is ensuring that exposed contacts are tested and antiretroviral treatment (ART) is offered immediately to people living with HIV (PLH), which not only reduces morbidity and mortality, but curtails onward transmission once viral suppression (VS) is achieved. The US Federal government has set a bold agenda to end the HIV epidemic, by reducing new HIV infections by 75% within five years and by 90% within ten years[38]. To succeed, early diagnosis, uptake of ART and sustained adherence need to be vastly improved, especially for PWID, who are underserved at every point in the HIV treatment cascade[39]. For example, by the end of Massachusetts' outbreaks in September 2018, only 63% of HIV-positive PWID

had achieved VS and 12% had not had a viral load test in the prior year, despite availability of state-supported health insurance[36]. Qualitative interviews with HIV-positive PWID revealed that many experienced frequent homelessness and incarceration, which are destabilizing factors that undermine ART adherence.

Pre-exposure prophylaxis (PrEP) has been shown effective in reducing HIV transmission among PWID[40]. The CDC recommends PrEP for PWID who are HIV-negative but have an HIV-positive or injecting partner of unknown serostatus and/or engage in sharing injection equipment[41]. Nationally, nearly one in five PWID are indicated for PrEP[42]. However, PrEP knowledge, access and uptake PWID remains abysmally low[23, 43-47], particularly in rural areas[48]. Uptake of PrEP among PWID in the US ranges from 0% to 5% in various studies and settings,[23, 43, 45, 47] despite high levels of interest and willingness[43-47]. Gender-based differences among PWID and PrEP knowledge and use need urgent study, as emerging research suggests integrating PrEP in SSPs may facilitate PrEP uptake[49]. Other reported barriers include low self-perceived HIV risk, concern about side effects, competing health priorities, and HIV stigma[49, 50].

A national survey conducted in 2013-14 among HIV care providers revealed that only 1% had prescribed PrEP to PWID,[51] perhaps due to concerns about adherence. However, a recent study of PWID revealed high HCV treatment adherence and viral clearance despite ongoing injection drug use[52], indicating that adherence barriers can be overcome. In 2015, nearly three-quarters of primary care physicians reported high interest in prescribing PrEP to PWID;[53] suggesting the provision of PrEP to PWID could be expanded. Formulations of

long-acting PrEP, such as injectable cabotegravir that has now been demonstrated to reduce HIV transmission, may provide a sustainable option for regular PrEP dosing for PWIDs,[54] provided that the psychological effects of receiving regular PrEP injections do not precipitate relapse or more frequent injection drug use.

Importance of Integrated OUD/ SUD treatment with HIV prevention and treatment:

Accurately screening for OUD, as well as other substance use disorders (SUDs), offering PrEP for those who are HIV-negative, and ART to those who are HIV-positive is essential for reducing ongoing HIV transmission. Substance use can interfere with ART adherence[55], which may impede VS, and increase risk of HIV transmission. Ongoing substance use can also increase the risk of acquiring HIV through condomless sex and contaminated injection equipment and may reduce PrEP adherence. Therefore, diagnosis and treatment of OUD/SUD is essential for optimizing HIV prevention and treatment.

MOUD is recognized as the most effective OUD treatment[56], and includes methadone, buprenorphine and extended-release naltrexone (XR-NTX). Numerous trials demonstrate that MOUD reduces opioid use, overdose, death, HIV and HCV transmission, and improved HIV VS and psychological well-being.[57-63] Recent research found that when MOUD was offered to PLH with OUD and alcohol use disorders upon release or prior to release from prison or jail, there was an increased likelihood of achieving and maintaining VS six months post-release.[59, 64, 65] Unfortunately, like the HIV treatment cascade, there are

substantial gaps in the OUD treatment cascade that begins with lack of OUD screening. Among those with an OUD diagnosis in the US, <20% are initiated on MOUD and <30% are retained on MOUD six months after initiation.[66]

To close the gaps for MOUD and HIV treatment in the US, the National Academy of Sciences, Engineering and Medicine (NASEM) recently convened a committee to evaluate integrated opioid and prevention services.[67] Barriers to integration of MOUD and HIV services included restrictive buprenorphine prescribing policies; burdensome prior authorization policies; lack of a motivated workforce; stigma and lack of expansion of MOUD, PrEP and other integrated services during and post-incarceration.

Yet integrated care for OUD and HIV is possible, and when offered, can improve VS among PWID.[59, 63, 64] In particular, the HIV Prevention Trials Network 074 trial demonstrated that integrating HIV and MOUD among PWID living with HIV who were randomized to receive an integrated intervention of behavioral support for SUD and ART resulted in greater self-reported ART adherence, VS, and MOUD uptake compared to standard of care[68]. Future research is needed to evaluate integrated MOUD with PrEP to reduce new HIV infections.

Resurgence of Stimulant Use

Although the US overdose crisis has been largely attributed to opioids, recent surveillance data from twelve US cities showed a resurgence in methamphetamine and cocaine use[69]. A recent CDC report estimated that 1.6 million adults reported using methamphetamine in the past year, 22% injected it, and over half had a methamphetamine use disorder[70]. In some US cities

(e.g., Atlanta and New York), urban African American populations that had primarily used heroin are increasingly shifting to methamphetamine and cocaine use in combination with heroin and fentanyl. Since methamphetamine and cocaine use are associated with high risk sexual behaviors[71, 72], there is concern that HIV incidence could surge in cities with high background HIV prevalence.

Treatment of methamphetamine use disorder has been hampered by the lack of an established pharmacologic treatment[73]. However, mirtazapine, a mixed monoamine agonist-antagonist that has been used to treat depression, has been hypothesized to reduce craving and withdrawal symptoms associated with methamphetamine use. Following an earlier trial that showed promise[74], a recent clinical trial of MSM[75] found that oral mirtazapine use was associated with greater number of weeks of abstinence, as well as decreases in number of male sexual partners and condomless sex. Efforts are needed to expand its use among PWID who have methamphetamine use disorders.

Lessons Learned

The US experience with ongoing HIV outbreaks among PWID offers several lessons for other countries. First, harm reduction services that offer SSPs and MOUD need to be widely implemented *before* outbreaks occur, which means that policymakers must learn to accept their public health imperative even when they object on moral grounds. Surveillance that relies on HIV testing alone may miss outbreaks until it is too late to intervene. In every setting which experienced rising incidence of acute HBV, HCV and endocarditis, SSPs and

over-the-counter syringe sales should be available and expanded. If patterns of dispersed hotspots become more common among rural and suburban communities, surveillance will need to be re-structured. Molecular epidemiology with new tools such as Nanopore MinION® can be implemented in real time to inform resource allocation during active outbreaks. Novel approaches such as monitoring drug metabolites in wastewater could also inform surveillance of drug use behaviors and corresponding gaps in MOUD[76].

When surveillance data uncover subgroups that are over-represented among PWID and PLH, public health actors need to spring into action. For example, in the US and elsewhere, women who inject drugs experience overlapping risk factors related to sex work, incarceration, gender-based and intimate-partner violence, all of which leads to risky injection and sexual practices, and ultimately increased vulnerability to HIV. To address these unique, gendered vulnerabilities, a multi-level, multi-tiered approach that integrates biomedical, structural and social prevention efforts is needed that considers gender-based violence, pregnancy, mental health, childcare, and post-release services.[77, 78]

The US experience has also uncovered 'deaths of despair[79]' that reflect syndemics with common underlying drivers: HIV, viral hepatitis, STIs, SUD and more recently, COVID-19. If the root causes of poverty, discrimination and stigma can be intervened upon, the end result could reduce the burden of HIV as well as other diseases that share similar root causes[80, 81]. Recently, validated scales that measure anticipated, enacted, and internalized stigma for people with SUD show promise for identifying intervention targets to reduce stigma related to substance use and MOUD[82].

The US experience also shows that providers, policymakers and even researchers have overlooked PWID and PrEP in the HIV treatment cascade. Based on the extremely low levels of awareness and coverage of PrEP among PWID and recent findings that long-acting cabotegravir is an efficacious PrEP modality[83], there is an urgent need for increased education about PrEP as an HIV prevention intervention in regions that are highly vulnerable for HIV outbreaks. However, it will be important to ensure that PrEP is offered as one component of the HIV prevention response and not in lieu of harm reduction services.

Without improving the continuum of care for MOUD, opioid use disorder and its consequences will continue to weigh heavily on society and health care systems. NASEM's recommendations to overcome these barriers[67] were recently summarized by co-author Springer and colleagues in a recent JAMA viewpoint[84] where it was recommended that structural barriers to MOUD and harm reduction programs be removed; funding be allocated to address the needs of low-income uninsured or under-insured individuals with OUD and HIV; workforce training on integrating OUD and HIV services should be improved; and timely access to health insurance, MOUD and PrEP be offered in criminal justice settings and upon release.

The US response to the HIV epidemic among PWID has been fractured. A crucial lesson for vulnerable communities is 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. Restructuring a path forward requires that evidence-based interventions be

integrated and brought to scale while simultaneously addressing underlying structural drivers. Failing to do so will mean that HIV outbreaks among PWID and the communities they live in will continue to occur in a tragic and relentless cycle.

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Conflicts of Interest

There are no conflicts of interest.

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