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The Past, Present, and Future of PrEP implementation Among People Who Use Drugs

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Abstract

Purpose of review—Recent HIV outbreaks among people who use drugs (PWUD) necessitate additional HIV prevention tools. Pre-exposure prophylaxis (PrEP) is highly efficacious yet uptake among PWUD remains exceedingly low. To address multilevel, complex barriers to PrEP use among PWUD, a range of intervention strategies are needed.

Recent findings—The literature on interventions to optimize PrEP use among PWUD is nascent, comprising small pilots and demonstration projects in early phases of intervention development. Initial studies suggest that structural, healthcare, interpersonal, and individual-level interventions can improve PrEP use for PWUD, and a number of efficacy trials are underway.

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Declaration

Ethics Statement All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Declaration of Helsinki and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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Summary—Future studies are needed to optimize the use of new PrEP modalities (e.g., injectable PrEP), simultaneously target multilevel challenges to PrEP use, and evaluate the integration of PrEP into other service settings and substance use treatment modalities.

Keywords

PrEP; HIV; Substance use; Stimulants; Opioids; Injection drug use

Introduction

HIV transmission among people who use drugs (PWUD) is a critical public health issue in the USA and globally. Drug use has been inextricably linked with HIV transmission since the emergence of the virus, with diverse populations of PWUD experiencing heightened burden of HIV acquisition through both injection and sexual exposures. In the USA and several other countries, recent increases in the prevalence of opioid and polysubstance use and injection have been linked to HIV outbreaks among PWUD that are stunting past and ongoing efforts to end the HIV pandemic. Additionally, the injection of opioids including heroin, as well as the omnipresence of illicitly manufactured fentanyl in some local drug supplies [1–10••], has increased transmission of hepatitis C virus (HCV) in many places [11–13], which is often associated with subsequent HIV outbreaks [14–17]. Importantly, despite high levels of public policy attention to opioids, recent US HIV outbreaks in PWUD have frequently involved stimulants such as methamphetamine and cocaine in addition to opioids [18, 19]. In fact, the use of methamphetamine through injection and non-injection routes of administration has also increased in several regions of the world over the past decade, with US methamphetamine-related hospitalizations rising by 245% from 2008 to 2015 and overdose deaths involving methamphetamine increasing fourfold from 2011 to 2017 [20].

HIV transmission risk behaviors are common and likely increasing among PWUD in many settings. PWUD are more likely to engage in sexual and injection-related behaviors that can transmit HIV, including condomless sex and syringe sharing [21–23]. Recent data from the US National Behavioral Surveillance Survey indicate that approximately three quarters of people who inject drugs (PWID) nationally report past-year receptive syringe sharing and/or condomless sex [24], and these overlapping risks for HIV transmission frequently co-occur [21], with PWID reporting low rates of consistent condom use during both vaginal and anal sex [24–26]. In addition to HIV risk behaviors, structural and community-level factors, such as poverty, homelessness, neighborhood-level violence, and drug-related arrests and incarceration, also contribute to “risk environments” conducive to HIV transmission, particularly for Black and Latinx PWUD [24, 27, 28••]. Many PWUD also experience multilevel barriers to engagement in healthcare and prevention services [29, 30], which are particularly relevant for racial/ethnic and sexual minority PWUD, who may experience multiple, intersecting forms of stigma and discrimination (e.g., racism, heterosexism, addiction-related stigma) in healthcare and social service settings [28–30, 31••, 32, 33].

Underlying causes for vulnerability to HIV among PWUD are complex, broad, and often originate beyond individuals’ scope of control. For example, fentanyl, identified in rising

quantities in local drug supplies, is associated with more rapid onset of withdrawal symptoms and increases injection frequency [10••, 34]. Additionally, the use of stimulants such as methamphetamine, which is increasingly common in many populations of PWUD including social networks of men who have sex with men (MSM) and heterosexual populations affected by opioid use disorder (OUD), leads to increased impulsivity, behavioral disinhibition, as well as engagement in condomless anal or vaginal sex, having sex with multiple partners, and other behaviors that increase the risk of HIV transmission [35]. In particular, with MSM comprising the group with the highest risk of HIV acquisition globally, the prevalence of methamphetamine use is estimated to be over 20 times higher than in the general population and, depending on the region of the USA, may be even more pervasive among racial/ethnic minority MSM, which can further exacerbate HIV disparities in this key population [36–39].

Current HIV Prevention Strategies for PWUD

Currently available HIV prevention options have had varying degrees of success in reducing HIV transmission among PWUD [40]. For PWID, access to sterile syringes via syringe service programs (SSPs), pharmacies, and other distribution mechanisms can help reduce injection-related HIV transmission [40]. Historically, these initiatives have had a dramatic impact on reducing HIV incidence among PWID. While sterile syringes alone do not protect against sexual acquisition of HIV, SSPs often distribute condoms and directly provide or facilitate access to other essential services (e.g., HIV testing and linkage to care). However, in many regions in the USA and other countries globally, access to sterile syringes is nonexistent or limited. Even where available, supplies of sterile syringes may be insufficient given the increasing demand due to increasing injection frequency [41].

Treatments for substance use disorder can indirectly reduce HIV incidence by reducing the transmission risk behaviors. For example, pharmacologic treatments for OUD (e.g., methadone, buprenorphine, and naltrexone) have been shown to be effective in reducing HIV incidence [42, 43]; however, in many regions of the USA and other countries globally, access to medications for OUD is severely limited [44, 45]. Furthermore, these medications cannot fully address the complex range of polysubstance use that accompanies OUD, and effective pharmacotherapies for psychostimulants such as methamphetamine remain allusive [46]: although a recent trial of naltrexone combined with bupropion (compared to placebo) yielded some promising results, even in the treatment group, the short-term response (no methamphetamine detected in urine over 12 weeks) was low (~14%), highlighting the need for additional prevention options [47, 48]. Additionally, behavioral treatments for substance use disorder, such as cognitive behavioral therapy and contingency management, have shown modest improvements in treating non-stimulant substance use disorders [49–51]. However, while behavioral activation therapy has shown initial promise for the treatment of methamphetamine use, the evidence on effective behavioral treatments for methamphetamine use remains limited [36, 52]. Moreover, polysubstance use has been shown to be negatively associated with treatment success, further limiting the impact of treatments for substance use disorder on HIV prevention [50, 53].

Theoretically informed behavioral HIV risk reduction interventions targeting both individual-level cognitive factors (e.g., knowledge, self-efficacy, behavioral skills) and interpersonal relationships (e.g., sexual and/or drug use networks) have demonstrated success in reducing condomless sex and sharing of injection equipment among PWUD [36, 54–59]. For example, a theory-based, peer-delivered social network intervention to promote safer injection behaviors was shown to be efficacious in reducing HIV and HCV transmission among PWID in Ukraine [60]. However, limited evidence exists on the impact of behavioral interventions on actual HIV transmission, and the need for intensive, specialized delivery of these interventions raises concerns about their scalability and sustainability, particularly in resource-poor settings [40, 54, 56].

Finally, improved antiretroviral therapies (ART) could support HIV prevention among PWUD, but continued efforts are needed to ensure widespread, sustained access and engagement for diverse populations. First, early and consistent use of ART among people living with HIV can reduce onward transmission to nearly zero [61–64]. However, this requires individuals to know their HIV status, be linked to care, and maintain excellent ART adherence. Additionally, post-exposure prophylaxis (PEP), a 28-day course of three ARTs started following known or suspected HIV exposures, is highly effective at halting infection; however, PEP requires immediate treatment (within 72 h of exposure) and must be used after each new exposure, which may not be feasible for PWUD with high levels of structural and social vulnerabilities [65, 66].

In summary, while there are important HIV prevention options available for PWUD, there is an urgent need for additional HIV prevention tools for PWUD in order to curtail the HIV epidemic, particularly in the context of the ongoing co-occurring opioid and polysubstance use epidemics.

PrEP Research with PWUD

Pre-exposure prophylaxis (PrEP) is a promising HIV prevention option for PWUD [67]. Currently formulated as a oncedaily oral antiretroviral regimen, PrEP has been shown to be efficacious in reducing HIV acquisition by 44–75% in RCTs in diverse settings, including among MSM, transgender women, heterosexual couples, and PWID [68–70]. Across all studies, efficacy improved dramatically (80–99%) among those who were optimally adherent to PrEP [71]. While the rates of PrEP use among PWUD broadly are unknown, PrEP uptake among US PWID has lagged far behind that observed in other groups (i.e., MSM). Similarly, while data on PrEP adherence among PWUD are scarce, studies suggest that adherence is linked to sociodemographic as well as structural and social factors including age, gender, injection patterns and types of drugs used, and incarceration and homelessness [72, 73••, 74, 75••, 76••]. Nevertheless, evidence from PrEP trials and prior studies of HIV and HCV treatment utilization demonstrate that with adequate support, PWUD can access and adhere to these medications [76••, 77–79].

Barriers to PrEP use among PWUD have been detailed elsewhere; in brief, they are multilevel, including challenges at the structural, healthcare system/clinical, interpersonal, and individual levels. At the structural level, key social determinants of health, including

transportation and housing instability, present critical barriers to accessing PrEP [30, 80••]. At the healthcare system/clinical level, complex and multistep PrEP protocols, decentralized healthcare systems, and provider stigma and low willingness to prescribe PrEP, especially for racial/ethnic minority individuals, present key challenges to PrEP use among PWUD [29, 81–83]. At the interpersonal level, HIV- and PrEP-related stigma within social networks can interfere with accessing and remaining on PrEP [30, 80, 82, 84••]. At the individual level, optimal PrEP use is stymied in part by limited PrEP knowledge [67, 85–89], inaccurate HIV risk perceptions, and low motivation to take PrEP [83]. These multilevel barriers to PrEP use among PWUD are disproportionately experienced by racial and ethnic minorities in the USA, resulting in racial and ethnic disparities in PrEP use and highlighting the need for interventions to promote PrEP use for PWUD who are multiply marginalized [90]. In order to address these multilevel challenges, a range of intervention strategies are needed. In the remaining sections, guided by the socioecological framework [91], we discuss the state of the science on PrEP interventions among PWUD and provide recommendations for directions for future research.

State of the Science: PrEP Interventions Among PWUD

To conduct a thorough review of the published literature on PrEP interventions, we used PubMed/MEDLINE to identify behavioral interventions with PrEP cascade outcomes published between 2010 (year of publication of first efficacy clinical trial of PrEP for HIV prevention) and 2020 that enrolled PWUD exclusively or reported on subgroup analyses with PWUD.

Structural-Level interventions

Structural interventions are primed for improving structural barriers to PrEP use among PWUD. As PWUD experience numerous challenges accessing traditional healthcare services, bringing PrEP care into community settings already frequented by these populations (e.g., SSPs, harm reduction, and drop-in centers) represents a promising way to reduce structural barriers to PrEP uptake. Roth et al. evaluated a single-arm demonstration project to link cisgender women who inject drugs to PrEP offered onsite at a Philadelphia-based SSP [92••]. Participants were screened for PrEP indications and, if interested, referred to immediate onsite clinical screening (i.e., blood draw to evaluate contra-indications for PrEP) and case management to facilitate access to PrEP through participants' own insurance or the drug manufacturer's co-pay assistance program. Participants who initiated PrEP could also choose between filling prescriptions onsite at the SSP instead of the pharmacy and receiving text message reminders before scheduled visits. Over 24 weeks, 80% of women had initiated PrEP; however, tenofovir levels in urine showed that < 10% had consistent PrEP use in the past week, 44% were retained in the study, and among those retained, only 60% remained in PrEP care at 24 weeks. Frequency of SSP access was positively associated with PrEP initiation and retention in care. Results from this study suggest that integrating PrEP care into SSPs and CBOs where PWUD access other services may improve PrEP initiation, but that additional supports are likely needed to optimize PrEP adherence and persistence.

Structural interventions can also be used to target individual-level barriers (e.g., mass media campaigns can target individuals' low PrEP knowledge). For example, McMahan et al. developed HIV prevention and PrEP promotion materials aimed at cisgender MSM and transgender individuals using methamphetamine in King County, WA [93••]. Materials were distributed in condom packs and by peer educators at LGBTQ-focused venues in the city. In a single-arm, pre- (n = 221) and 9-month post- (n = 100) serial cross-sectional study, they found that PrEP awareness was near universal before (96%) and after (98%) the marketing campaign; however, a lower percentage of people surveyed at follow-up were concerned about PrEP *not* being effective to prevent HIV transmission (20% vs. 6% at baseline, $p <$ 0.01). Moreover, there was a higher percentage of people surveyed at follow-up that reported ever using PrEP compared to baseline (21% vs. 3%, respectively, $p < 0.01$), and prior PrEP use reported at follow-up was marginally associated with reporting seeing the promotion materials ($p = 0.05$). Notably, based on an experimental survey, Calabrese et al. suggest that inclusive framing of PrEP in public messaging (e.g., not targeting MSM or PWUD specifically) would facilitate access to PrEP by reducing stigma associated with HIV and PrEP use [94].

Healthcare System/Clinical-Level Interventions

The standard of care for PrEP requires an initial visit with a prescribing clinician that includes blood work to rule out acute HIV and kidney function, often followed by a brief delay while laboratory tests are processed and before PrEP is prescribed. For PWUD facing structural and social vulnerabilities, this timeline can be difficult and present barriers to uptake. Some health centers have begun to streamline this process and offer "low-threshold" care and same-day PrEP starts. For example, Boston Healthcare for the Homeless Program (BHCHP), a federally qualified health center offering a wide range of health services to people who use drugs and experience homelessness, implemented a novel PrEP program in 2018 in response to the rising numbers of new HIV infections identified locally [95••]. Their clinical innovations to improve PrEP access for this population included same-day PrEP prescribing, coordination with their onsite pharmacy, and storage lockers for medication. Additionally, to address stigma, this "low-threshold" model included leadership support for "PrEP champions" advocating for PrEP among prescribers across the center as well as the provision of a dedicated, culturally competent PrEP nurse and navigator. In the first 17 months of this program, BHCHP linked 239 PWUD to PrEP services and prescribed PrEP to 152 patients (mean = 8.9/month), over twice the rate of previous PrEP prescribing (n = 48; mean = 4/month). Moreover, there was a 44% (95% CI, 36–52%) cumulative probability of remaining on PrEP for 6 months during this timeframe. Similarly, Taylor et al. describe the successful implementation of a "PEP to PrEP" protocol for patients within a low-barrier substance use disorder "bridge clinic," providing PEP within a short window after potential HIV exposure and transitioning to PrEP immediately following completion of the PEP regimen [10••]. These initial examples suggest that PWUD can successfully engage in PrEP care when it is provided in accessible settings with appropriate supports from non-judgmental providers.

Interpersonal-Level Interventions

While stigma experienced in healthcare settings may be best addressed at the clinical and provider levels, HIV and PrEP stigma within social networks may be best addressed by intervening with peers and social networks directly. Diffusion of innovations theory posits that information and innovations are often spread through social networks, and as such, interventions that capitalize on these networks and the relationships within them can reduce stigma around behaviors and help accelerate adoption of new technologies such as PrEP [96]. Decades of peer- and social network–based interventions to improve HIV care engagement among PWUD living with HIV have demonstrated mixed results [97], and to date, limited network interventions have been tested to reduce PrEP-related stigma and increase PrEP use overall [98, 99], with even fewer studies adequately targeting PWUD. In one such example, Blackstock et al. piloted an intervention involving training peers to provide PrEP education and counseling to women (> 80% of whom reported recent drug use) at mobile SSPs and sex worker drop-in centers with navigation to PrEP care at external clinics [100••]. Of the 52 participants, only 25% scheduled and 6% attended an initial PrEP appointment (and none were prescribed PrEP), again suggesting important structural barriers for women who use drugs in accessing PrEP care and the need for multifaceted interventions to target multilevel barriers.

Individual-Level Interventions

Individual-level interventions primarily focus on cognitive, behavioral, or social processes of individuals, for example, by increasing knowledge, motivation, skills, and self-efficacy [101]. In order to improve PrEP uptake among PWUD, this may take the form of education on PrEP efficacy, side effects (and lack of known drug interactions), and availability, aligning perceived HIV risk with true risks based on patient-centered discussions of behavioral and structural risks; motivational interviewing; providing problem-solving and guidance on adherence strategies (or incentivizing optimal adherence, e.g., through contingency management); and using counseling to overcome psychosocial challenges that might impede PrEP use [80••].

Given that accurate knowledge of PrEP has been shown to be low among PWUD, education remains an important component of any PrEP intervention. Getty et al. conducted a pilot single-arm computer-based education intervention to increase knowledge about HIV and PrEP among 11 adults in Baltimore, MD, who were participating in an efficacy trial of contingency management for opioid and stimulant use [102••]. Four content areas (i.e., information about HIV transmission, signs and symptoms of HIV/AIDS, clinical indications for PrEP, and PrEP effectiveness) were covered in 33 modules. In pre-post comparisons, the proportion of participants with correct knowledge increased between 60 and 140% across all content areas. While this was a small pilot with short-term follow-up (and feasibility across real-world samples of PWUD based on computer access likely varies), it demonstrated low initial PrEP knowledge as well as the possibility of increasing it using a low-resource, computer-based intervention.

Some examples of more intensive interventions to improve adherence and persistence also exist. Shrestha et al. adapted the Community-Friendly Healthy Recovery Program (CHRP),

an HIV risk reduction intervention for high-risk PWUD informed by the information–motivation–behavioral skills model, to improve PrEP adherence [103, 104]. The resulting intervention was delivered over 4 weekly 50-min group sessions focusing on information about HIV and PrEP, motivation for PrEP adherence, and behavioral skills related to PrEP adherence, condom negotiation, and potential PrEP stigma management. The intervention also included one-way text message adherence reminders. Forty adults who had initiated PrEP within the past month, reported recent sexual or drug use–related HIV risk behaviors, had a clinical diagnosis of OUD, and were enrolled in methadone program participated in a single-arm pilot intervention. Both feasibility and acceptability were high—90% completed all four group sessions, and > 95% reported high satisfaction. Moreover, self-reported PrEP adherence and PrEP-related knowledge, motivation, and behavioral skills improved significantly over follow-up and persisted 1-month post-intervention. Studies such as this suggest that interventions to increase PrEP knowledge, motivation, and behavioral skills have the potential to improve PrEP utilization among PWUD.

Conclusions

PWUD are at an elevated risk for HIV infection and should be considered high priority for PrEP implementation. However, they also face complex and multilevel barriers to PrEP initiation and continued and optimal use. While uptake has been low thus far, there is reason for optimism—initial studies suggest that structural, healthcare system/clinical, interpersonal, and individual-level interventions can improve PrEP use for PWUD. While many of these studies were small pilots or demonstration projects representing early phases of intervention development and testing (e.g., lack of control arm, insufficient statistical power), data from NIH Reporter and a search of published protocols suggest that results of full-scale efficacy trials are on the horizon [105••, 106••, 107••, 108–114]. Rigorous randomized controlled trials and implementation studies are necessary to assess the efficacy and effectiveness of these behavioral interventions to improve the PrEP cascade among PWUD. Based on the known barriers to PrEP uptake and apparent gaps in the PrEP intervention science for PWUD, we advocate for future studies in the following areas:

A. ***Expanded research on new PrEP modalities and other biomedical HIV prevention strategies in the development pipeline that better engages PWUD.*** While at various stages of development, trials of new HIV prevention strategies, including long-acting PrEP (e.g., bimonthly injections, annual implant, infusion of broadly neutralizing antibodies), have shown promising results [115–118]. While these modalities may reduce or eliminate some of the challenges with daily medication adherence experiences among PWUD, and studies have shown that PWUD would be willing to use them, trials of these products to date have largely excluded PWUD [83, 119]. This exclusion will continue to sow doubt about the appropriateness of PrEP for PWUD, and it is essential that PWUD with diverse sociodemographic and substance use profiles are better engaged in future trials and subsequent phases of research on “next-generation” PrEP products.

B. ***Multifaceted interventions that address multilevel challenges simultaneously.*** The use of innovative intervention research designs such as the multiphase

optimization strategy can allow the efficient determination of which intervention components best optimize efficacy and which should be refined or eliminated [120]. These designs could be beneficial for determining the best combinations of strategies for diverse PWUD, forms of substance use, and clinical settings while maintain methodological rigor.

C. ***Interventions addressing intersecting stigmas.*** Given the disproportionate impact of HIV on Black and Latinx PWUD, it is imperative that interventions, both behavioral and biomedical, address these inequities by targeting the structural factors, such as discrimination, implicit bias, and medical mistrust, which lead to them. Modeling studies have shown that PrEP can lead to a reduction in overall HIV incidence and in racial/ethnic disparities in HIV incidence but that this will only occur with targeted approaches [121–123].

D. ***Provider-level interventions to improve PrEP prescribing to PWUD.*** Data continues to demonstrate that providers are less willing to prescribe PrEP to PWUD despite their high levels of need (81, 113); as such, interventions that simultaneously address PrEP guideline education, streamlined PrEP protocols, and addiction-related stigma should be prioritized [84, 124, 125].

E. ***Integration of PrEP into harm reduction and substance use disorder treatment services and facilities.*** While studies are underway examining the efficacy of multicomponent PrEP interventions provided within syringe service programs and methadone clinics [108, 112], future studies are needed to understand the potential bundling of PrEP within other service settings and for different substance use behaviors (e.g., considering new treatments for stimulant use disorders). These programs will need to consider the type of substance use and polysubstance use in order to ensure appropriate treatment bundles.

F. ***Implementation research on “low-threshold” care models.*** Given that many community health centers, harm reduction and other service organizations, and health departments have already begun integrating PrEP into their service delivery models, implementation studies are needed to identify the key components of successful “low-threshold” PrEP service delivery models (e.g., PrEP navigation, same-day and onsite PrEP prescriptions) [10, 95]. Implementation studies are also needed to help support organizations’ efforts by evaluating the impact of these strategies and disseminating best practices regarding supporting PWUD with PrEP uptake, adherence, and persistence.

G. ***Rapid PrEP distribution, particularly in contexts of new HIV outbreaks and clusters.*** Given the ongoing opioid and polysubstance use epidemics in the USA and many countries globally, innovations in rapid PrEP distribution in the contexts of HIV outbreaks and clusters are urgently needed. For example, studies could test the efficacy of scaling up of “PEP to PrEP” models and pharmacy-delivered PrEP [10••, 126, 127]. These efforts could have immediate impacts on “getting to zero.”

H. ***Global research supporting PrEP delivery to diverse populations of PWUD.*** As evidenced by this review, there is a dearth of interventions to enhance PrEP use among PWUD outside of the USA. Given the widespread yet distinct epidemiology of drug use across regions and countries globally, it is essential that interventions are implemented in diverse settings with established as well as emerging drug markets where PrEP holds promise [128, 129].

In conclusion, PWUD have been disproportionately impacted by HIV since the beginning of the epidemic, and sustained research, work, and advocacy by diverse community, research, and policy stakeholders have been crucial to shaping the public health response toward evidence-based strategies to address the epidemic. However, gaps in the scientific knowledge persist, and political opposition to harm reduction-oriented, rights-based practice and research is still common in the USA and worldwide. Development, evaluation, and implementation of a comprehensive research and policy agenda to support PrEP use among PWUD will require concerted efforts across these stakeholders. Such a diverse coalition may prove essential in realizing the potential of PrEP and other behavioral and biomedical interventions to curb HIV transmission and reduce health disparities among PWUD.

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