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The Pre-Exposure Prophylaxis (PrEP) Care Cascade in People who Inject Drugs: A Systematic Review

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Abstract

Injection drug use is a key risk factor for the transmission of HIV. Prevention strategies, such as the use of pre-exposure prophylaxis (PrEP), are effective at reducing the risk of HIV transmission in people who inject drugs (PWID). Following PRISMA guidelines, a literature search was conducted to identify the current state of the PrEP care cascade in PWID. Twenty-three articles were evaluated in this systematic review. A decline in engagement throughout the stages of the PrEP care cascade was found. High awareness and willingness to use PrEP was found, yet PrEP uptake was relatively low (0–3%). There is a lack of research on interventions to increase engagement of PrEP across all levels of the care cascade in PWID. Implications from the interventions that have been published provide insight into practice and public policy on efficacious strategies to reduce HIV incidence in PWID. Our findings suggest that more efforts are needed to identify and screen PWID for PrEP eligibility and to link and maintain them with appropriate PrEP care.

Keywords

Pre-exposure prophylaxis (PrEP); HIV prevention; people who inject drugs (PWID); PrEP care cascade; systematic review

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Introduction

Injection drug use is a significant public health issue, increasing the risk for infectious disease transmission, such as HIV [1]. People who inject drugs (PWID) accounted for 9% of all new HIV diagnoses in the United States in 2017; of those 3,641 diagnoses, 34% were identified among men who have sex with men (MSM) [2]. High rates of injection stimulant use among MSM who inject drugs have contributed to an increase in HIV incidence [3]. The ongoing opioid epidemic has also contributed to the rise in HIV incidence among PWID, as HIV transmission has been linked with opioid use disorder [4]. The Centers for Disease Control and Prevention (CDC) recognized PWID, alongside MSM and heterosexual females, as a priority population for HIV prevention efforts, given their disproportionate burden of annual HIV infections [2]. In addition to sex-related risk behaviors, PWID pose unique drug-related HIV risks via sharing needles, syringes, and other injection equipment [1].

While PWID display higher drug-related risk behaviors than other substance users, it is also important to recognize the increase in sex-related risk behaviors (e.g., condomless sex, transactional sex) in this group [5]. HIV outbreaks often occur in social and geographical networks of PWID [6]. Evidence-based harm reduction programs, such as syringe services programs (SSP) and opiate agonist therapies (OAT), have been effective in reducing HIV outbreaks among PWID. Access to and utilization of such programs, however, remains limited or unavailable [7–10]; sexual and injection-related HIV risks persist in many PWID. Given the potential for future outbreaks amid the ongoing opioid crisis, there is an urgent need for innovative prevention strategies to address the intersectional drug- and sex-related risk behaviors in the population [5].

Historically, prevention strategies for HIV in PWID have focused primarily on behavioral interventions (e.g., condom use, abstinence, SSP, OAT) [11]. PrEP represents an important biomedical advancement for HIV prevention that, when taken properly (daily), can prevent the transmission of HIV in PWID [12, 13]. The PrEP care cascade provides measurable milestones used to track the progress, starting from identifying individuals at risk for HIV infection to persistence in PrEP care [14]. It is analogous to the HIV treatment cascade, particularly in terms of identifying at-risk populations and the consecutive stages of treatment initiation and adherence. Identifying at-risk individuals and screening them for PrEP eligibility are the first steps in the preventative framework. The last stages in the cascade include linking individuals to care, followed by the adherence and persistence in PrEP care services. All stages can be influenced by behavioral interventions designed to increase engagement throughout [14].

In the only clinical trial to examine PrEP efficacy among PWID, the Bangkok Tenofovir Study, Choopanya et al. found a 48.9% reduction in HIV incidence for the experimental group taking PrEP, compared to the control group not taking PrEP. In a separate analysis, the risk was reduced by approximately 74% in participants with detectable levels of tenofovir [13]. Consequently, the CDC recommended the use of PrEP among PWID, alongside MSM and heterosexual females, [12]. Studies on PrEP in MSM have indicated alcohol and stimulant drugs to be a barrier to PrEP adherence [15–18]. Only one study was found

comparing awareness of PrEP between MSM and PWID [19] and two studies with female sex workers who reported injection drug use as participants [20, 21]. PrEP is particularly beneficial for subgroups of PWID, given its ability to protect from HIV transmission through both drug-related and sex-related behaviors [5].

Despite the efficacy of PrEP at preventing HIV, reluctance to initiate it has been observed in PWID [22]. A majority of studies on PrEP in PWID focus on the beginning stages of the PrEP care cascade, such as increasing awareness, knowledge, and willingness to use PrEP. Sophus and Mitchell (2019) highlight the difference in PrEP awareness (being aware of PrEP as a tool to prevent HIV infection) from PrEP knowledge (knowing specific information about PrEP – such as efficacy, side-effects, dosage, etc.). Both awareness and knowledge are necessary to increase one's willingness to use PrEP. Willingness to use PrEP is defined as one's self-motivation to initiate and adhere to PrEP [23]. Relatedly, risk perception is a variable that contributes to the willingness to use PrEP among individuals who do not perceive themselves at risk for HIV and are, therefore unlikely to engage in PrEP services [24]. Researchers have identified the importance of PrEP awareness, knowledge, and willingness to use as precursors for PrEP use and adherence [25].

The last stage of the PrEP care cascade addressed in this review is PrEP use and adherence. Even if individuals demonstrate high awareness, risk perception, and willingness to use PrEP, various barriers may reduce uptake and adherence [20]. Barriers to PrEP uptake include multi-level factors, including patient- (e.g., low perceived HIV risk, competing priorities, concerns about side-effects and drug interactions, negative experiences with clinicians), provider- (e.g., distrust of clinicians and drug use-related stigma), and structural-level (e.g., transportation difficulties, centralized PrEP prescription) [20–23, 26–32].

The purpose of this study is to review the current literature on the six PrEP care cascade variables identified above (e.g., awareness, knowledge, risk perception, willingness to use, access to HIV professionals, PrEP use, and adherence) among PWID. Findings will be integrated into the PrEP care cascade framework and used to provide empirical evidence to inform future research and practice in this area.

Methods

Literature Search

Following PRISMA guidelines, a comprehensive literature search was completed using the following databases: PubMed, PsycInfo, and CINAHL. Search terms in PubMed included ("Substance Abuse, Intravenous" [Mesh] OR "people who use drugs" OR "sex workers" OR "women who use drugs" OR "men who have sex with men who use drugs" OR "injection drug use" OR "opioids" OR "opioid use disorder" OR "chemsex") AND ("PrEP" OR "Pre-Exposure Prophylaxis" [Mesh]). Search terms used in PsycInfo and CINAHL included ("pre-exposure prophylaxis" OR "prep" OR "pre-exposure prophylaxis") AND ("pwid" OR "people who inject drugs" OR "people who use drugs" OR "sex workers" OR "women who use drugs" OR "women who inject drugs" OR "men who have sex with men who use drugs" OR "injection drug use" OR "opioid use disorder" OR "chemsex").

For the search of ongoing or future PrEP studies on PWID, we used the search terms “PrEP” AND “people who inject drugs” AND “HIV prevention” AND “United States” in clinicaltrials.gov. Additional screening was conducted for the search terms “female sex workers” AND “PrEP” AND “injection drug use” AND “United States.” A final search was conducted using the search terms “men who have sex with men” AND “PrEP” AND “injection drug use” AND “United States.” A secondary search was also conducted that involved checking the reference sections of relevant review papers for articles that were not found in the initial computerized search.

Study Selection and Inclusion/Exclusion Criteria

Published articles were retained if they included participants who used injection drugs; used qualitative and/or quantitative measures on PrEP awareness, PrEP knowledge, willingness to use PrEP/ intent to use PrEP/ PrEP acceptability, PrEP use, HIV risk perception, barriers to PrEP use, and/or access to HIV professionals, and were peer-reviewed and published in English from 2013–2020. Articles were excluded from this review if they did not include any outcomes along the PrEP care cascade; did not include measures on PWID; focused on the cost-effectiveness of PrEP implementation in PWID; were a systematic review; and/or were not performed on participants in the United States. For data analyses, the “heard of PrEP” and “aware of PrEP” variables were collapsed into one variable, referenced as “PrEP awareness.” Similarly, the “PrEP acceptability,” along with the “willingness to use” and “intent to use” variables were collapsed into one variable referenced as “willingness to use PrEP.” No other variables were collapsed for data analyses.

Results

Three hundred and sixty-six articles were found in the initial search of PubMed (n = 131), CINAHL (n = 146), and PsycInfo (n = 89). Six additional articles were found upon reviewing references of relevant articles. After duplicates were removed, we included a total of 105 articles to review for further assessment of inclusion criteria. Upon reviewing abstracts, an additional 78 articles were excluded for: being conducted outside the United States (n = 51), not including PWID as participants (n = 9), not including PrEP variables, (n = 7), and being systematic reviews (n = 11). The remaining 27 full-text articles were reviewed, and four studies were excluded because of their focus on the cost-effectiveness of PrEP. Due to the low rates of PrEP use and adherence in PWID, none of the studies reported on ‘persistence in PrEP care’. Therefore, we were not able to examine this as an outcome in our review. A total of 23 peer-reviewed articles were included in the systematic review (Figure 1).

Study Characteristics

Table 1 contains an overview of the studies and demographics of the included 23 studies. Most of the participants in the included studies reported injection drug use within the past six months and currently prescribed methadone. Most participants reported being middle-aged, ranging from an average of 30 to 45 years old. Aside from the four studies, including only female participants [20, 21, 32, 33], the other studies had more male participants than female. More than half of participants from all studies reported being White/Caucasian

except for three studies [33–35]. The majority of the participants reported a low educational level (no college graduates), and low annual income (< $9,999/year). Homelessness ranged from 28 to 75%. All studies had a majority of participants who identified as heterosexual, except for one [19]. All results were from participants recruited from a community-based organization (CBO), SSP, or OAT, or data was collected as part of the National HIV Behavioral Surveillance (NHBS) on people who reported injection drug use. Twenty-one of the twenty-three studies were conducted on the East Coast [19–23, 27–42], while one was performed in West Virginia [26]. McFarland et al. (2019) was the only study conducted on the West Coast [43].

PrEP Care Cascade

PrEP Awareness—The sample size from the 19 studies [19–23, 26, 27, 29, 31, 33–38, 40–43] that measured PrEP awareness ranged from 16 [20] to 612 participants [37] (Table 2). PrEP awareness ranged from >1% (n = 1/118) to 57% (n = 227/398) across studies [33, 43]. No significant difference in PrEP awareness was found between ethnic groups in a sample of 138 adults with OUD in New York [36]. McFarland et al. (2019) found women who inject drugs (WWID) to be significantly more aware of PrEP than men who inject drugs, in a study of 398 PWID on the West Coast [43]. Similar findings were reported by Roth et al. (2019) in a quantitative analysis among 612 PWID on the East Coast [37]. Factors associated with PrEP awareness in a multiple regression analysis of the same 612 PWID included: identifying as LGBTQ, having a college education, attendance at a drug treatment facility, receiving an STI test, sharing paraphernalia, and/or visiting an SSP [37].

In a quantitative study conducted by Walters et al. (2017a) in New York City, increased PrEP awareness was associated with the use of an SSP and/or reported transactional sex in a sample of 118 WWID [33]. In another quantitative study, Walters et al. (2017b) compared PrEP awareness in 664 male and female participants who inject drugs and 793 MSM participants [19]. When controlling for demographic variables, HIV status, cocaine and heroin use, and exposure to HIV prevention professionals, Walters et al. (2017b) found both males and females who inject drugs to have decreased odds of PrEP awareness compared with those of MSM. Participants from the same study who had significantly higher odds of PrEP awareness included those with exposure to health professionals, were HIV-infected, reported cocaine and heroin use, and higher household income [19].

In terms of geographical differences, the highest percent of PrEP awareness from qualitative studies on the East Coast was 36% (n = 12/33; [22, 27]). Similar results were found by Peitzmeier et al. (2017) in a quantitative study among 60 female sex workers who reported injection drug use on the East Coast, with 33% (n = 20/60) of participants reporting PrEP awareness [21]. McFarland et al. (2019) found 57% (n = 227/398) of participants in a quantitative study to be aware of PrEP, among a sample of 398 PWID on the West Coast. [43]. PrEP awareness in rural West Virginia was reported from 33% (n = 16/27) of participants who inject drugs in a mixed-methods study by Allen et al. (2019) [26].

PrEP Knowledge—The sample size from the five studies [20, 27, 29, 39, 43] that measured PrEP knowledge ranged from 16 [20] to 398 participants [43]. PrEP knowledge

was reported by less than 40% of participants from all studies; the greatest percent of participants with PrEP knowledge (39%; n = 155/398) was reported by McFarland et al. (2019) in a study performed on the West Coast [43]. Yet, Footer et al. (2019) found only 13% (n = 5/16) of participants to have PrEP knowledge, in focus groups conducted among 16 WWID on the East Coast [20]. Bazzi et al. (2018) conducted semi-structured interviews with 33 PWID in Boston, MA, and found those who more willing to use PrEP had knowledge of PrEP prior to engaging in the study [27]. Among a sample of 40 opioid-dependent persons enrolled in substance abuse treatment, Shrestha et al. (2018) found that an integrated bio-behavioral HIV prevention approach was successful at increasing PrEP-related knowledge [39].

Risk Perception—The sample size from the 5 studies [20, 23, 32, 41, 42] that measured HIV risk perception ranged from 16 [20] to 400 participants [20, 23, 41, 42]. Risk perception ranged from 1.1% (n = 4/351) of participants [23] who perceived themselves at very high risk for HIV to 66% (n = 264/400) of participants who perceived themselves to be at risk for contracting HIV [41, 42]. Footer et al. (2019) conducted qualitative focus groups among 16 WWID in Baltimore and found 18% (n = 3/16) of participants reported “never having worried about contracting HIV”, despite frequent injection drug use [20].

Willingness to use PrEP—The sample size of the 14 studies [21, 22, 26–28, 31, 34–36, 38, 40–42, 44] that measured willingness to use PrEP ranged from 33 [22, 27] to 400 participants [38, 40–42]. Themes from a qualitative analysis identified subgroups of 33 participants more willing to use PrEP. In a qualitative analysis, Bazzi et al. (2018) found participants, in Boston, who acknowledged their HIV risk to also report knowing PLWH, having engaged in risky sexual behavior, and sharing drug paraphernalia. Participants from the same study who were less willing to use PrEP acknowledged a low-risk perception for HIV, not sharing drug paraphernalia, or that HIV prevention was not a priority [27]. In a separate qualitative analysis of the same sample of 33 PWID, Biello et al. (2018) found appropriate support services (e.g., social support, support from the clinicians) would increase willingness to use PrEP [22].

In New Jersey, Roth et al. (2018) found females to be more willing to use PrEP, compared to males, in a quantitative study of 138 PWID [28]. Females were also found to be more likely than men to report a willingness to tolerate adverse effects of PrEP and quarterly HIV testing in the same sample [28]. In another quantitative study of 265 PWID in Baltimore, Sherman et al. (2019) found homelessness, being PrEP eligible, and having other medical diagnoses to be associated with willingness to use PrEP [35]. Kuo et al. found other variables related to PrEP willingness that included: identifying as bisexual, screening positive for depressive symptoms, having two or more sex partners in the past 12 months, and injection cocaine use; in a study of 304 PWID in Washington, D.C. In a multivariate analysis of the same dataset, researchers found being less than 50 years old and sharing drug paraphernalia to be associated with willingness to use PrEP [34]. Jo et al. (2020) recruited 304 PWID from Florida’s first legal SSP and found participants who reported only injecting opioids had decreased odds of willingness to use PrEP compared to polysubstance injection users [31].

In a quantitative analysis, Shrestha et al. (2017) found that information, motivation, and behavioral skills (IMB) determinants predicted willingness to use PrEP among a sample of 400 people with OUD, enrolled in a Methadone Maintenance Program (MMP) in New Haven, CT [38]. In a separate analysis of the same dataset, neurocognitive impairment (NCI) and higher perceived HIV risk were associated with willingness to use PrEP [41]. Further, an indirect effect of NCI on willingness to use PrEP via HIV risk behavior was found, among the same sample of 400 participants in treatment for OUD [42].

Access to HIV health care providers—The sample size of the 11 studies [19–22, 26, 28, 30, 31, 36, 37, 43] that measured access to HIV health care professionals ranged from 16 [20] to 612 participants [37]. Participants from 9 studies reported attendance at CBO, SSP, or addiction treatment setting as their primary venue for accessing primary HIV prevention services. In a quantitative study of 138 participants, Roth et al. (2018) found, 86% (n = 119/138) of participants reported they would prefer to access to HIV testing in SSP than traditional STI testing centers [28]. Explicitly, a mobile testing van was found to be the most preferred venue for HIV testing (73%, n = 108/138) for participants in the same study [28]. Similarly, in a study of 40 people with OUD, who had initiated PrEP and were enrolled in an MMP, 55% (n = 22/40) were prescribed PrEP from a clinician at the addiction treatment setting and 14% (n = 6/40) at the mobile healthcare van [30].

In a quantitative study performed in Philadelphia, PA by Roth et al. (2019), only 18.4% (n = 14/612) of the PWID who were aware of PrEP reported discussing PrEP with a healthcare provider [37]. In a separate quantitative study, conducted in San Francisco, participants who identified as MSM were more likely to have discussed PrEP with a healthcare provider than non-MSM PWID [43]. Jo et al. (2020) found that only 5.7% (n = 2/157) of participants recruited in Miami had requested appointments with a PrEP provider after learning about their PrEP eligibility [31].

PrEP use—The sample size of the 10 studies [22, 27, 29, 34, 37, 38, 40–43] measuring PrEP use ranged from 20 [29] to 612 participants [40–42]. Overall, the uptake of PrEP among PWID was found to be considerably low, ranging from non-existent [34] to 3% (n = 3/33 [22, 27]) (n = 12/398 [43]). In the one study performed on the West Coast, McFarland et al. (2019) found all 7 PWID who had used PrEP in the past year identified as MSM [43]. After excluding MSM in data analysis of the same sample, females were more likely than males to have used PrEP in the past year [43].

PrEP adherence—The high adherence rate for participants on PrEP is an important element to highlight when considering promoting PrEP uptake among PWID. Only one study, by Shrestha et al. (2018), utilized a structured intervention to increase PrEP adherence and PrEP-related knowledge in PWID in New Haven, CT [39]. The bio-behavioral intervention consisted of four weekly one-hour modules utilizing verbal, visual, and interactive strategies to inform participants. An increase in self-reported PrEP adherence was noted immediately after and at a one-month post-intervention. All 40 participants reported the continued use of PrEP throughout the study; however, data are not yet available beyond the one-month follow up [39].

Discussion

The current review provides an updated examination of the PrEP care cascade in PWID. Results from this review support conclusion from the National Institute of Mental Health (NIMH) (2015) describing the PrEP care cascade and the urgency to increase PrEP knowledge, linkage to care, and uptake in PWID to reduce the incidence of HIV transmission [14], amidst the ongoing opioid epidemic. Research on PrEP in PWID began in 2013, shortly after FDA approval and CDC recommendations [12]. The limited research on the topic is a concern and must be expanded. The 23 articles included in this systematic review were the only found articles, including variables on PrEP among PWID in the United States.

The findings from this review indicate a need to intervene appropriately at each phase of the PrEP care cascade in PWID. Although a high willingness to use PrEP was found across studies, the presence of multi-level barriers seems to impact PrEP uptake in PWID significantly. Linkage to care should be prioritized as an intervention strategy in bridging the gap between willingness to use PrEP and PrEP uptake [19–22, 26, 28, 30, 36, 37]. In addition, barriers impeding engagement at each phase of the PrEP care cascade should be addressed. Barriers to PrEP use included lack of knowledge, perceived drug interactions/side effects, homelessness, cost, adherence, and access to healthcare professionals [20–23, 26–32]. Various types of stigma - stemming from health care providers, peers, and family members - was the most consistent barrier at all stages [20–23, 26–31]. The effects of intersectional HIV and drug use stigma on PrEP uptake may provide a greater understanding of reluctance to use PrEP in PWID [45].

Future Research and Practice

While PrEP awareness and uptake in MSM have increased in the past six years [46], PWID are less likely to acknowledge and use PrEP as an HIV prevention strategy [19]. PrEP interventions for MSM highlight the continued need for condom use to prevent STI transmission [47]. Harm reduction strategies tailored to MSM can provide valuable insight into interventions targeting PrEP use in PWID, such as safe sex practices. An interesting finding in our study was the anticipated continuation of risky behaviors in PWID who were willing to use PrEP [21, 22, 29, 34, 38, 41]. The continued engagement in risky sex and drug-related behaviors in this population highlights the need to focus on establishing/maintaining harm reduction strategies (e.g., needle cleaning, condom use) while on PrEP.

Most research on PrEP in PWID was conducted in cities along the coasts of the United States, with only one located in a rural location. As the opioid epidemic continues to affect rural areas disproportionately, PWID in rural settings are particularly at risk for HIV [26]. Endorsement of SSP varies by state policy, limiting accessibility to HIV prevention services, particularly in rural areas [48]. More legislative action is needed to support funding and staffing for SSP that can impact HIV transmission in PWID [48]. Innovative strategies to inform and link PWID to PrEP services, such as mobile healthcare vans, must be greater explored to reduce HIV incidence in this population [19–22, 26, 28, 30, 36, 37]. More research on efficacious bio-behavioral interventions is also needed to increase adherence to PrEP among PWID in order to address their reluctance to initiate and adhere to PrEP.

Future studies should investigate PrEP awareness and linkage/persistence in care among PWID. Potential strategies to improve the PrEP care cascade in PWID include the integration of HIV services in existing harm reduction programs [19–22, 26, 28, 30, 36, 37]. Common drug treatment settings (e.g., MMP) and SSP increase accessibility of evidence-based harm reduction programs to this high-risk group, and an opportunity to intervene. Mobile community-based vans can be utilized to provide basic care, accurate information, and link PWID to HIV-focused care [19–22, 26, 28, 30, 36, 37]. Although integrating HIV and MMP services is an evidence-based practice, lack of staffing or funding often reduces implementation in real-world settings [49, 50]. A challenging subpopulation of PWID to reach are those who are 'out of care' and do not attend drug treatment or harm reduction services. Specific intervention techniques tailored to this subpopulation are needed at all stages of the PrEP care cascade in order to reduce HIV transmission.

Because high rates of PWID are among those who identify as MSM and/or are an ethnic/racial minority [1], adding culturally sensitive service care providers into existing programs may increase willingness to engage in HIV prevention in this particularly at-risk population. The integration of PrEP eligibility screening and linkage to medical providers into SSP could increase accessibility and treatment engagement through an integrated healthcare model [51]. Mental health has been identified as a barrier at all stages of the HIV care continuum [52], and likely to limit PrEP engagement in similar contexts. Given the greater prevalence of mental health conditions among PWID, and sexual/racial/ethnic minority populations [45, 53, 54], there is a need to simultaneously intervene on numerous factors influencing engagement in HIV prevention services. Adapting an integrated care model into SSP and MMT facilities is likely to address the complexity of factors limiting PrEP use in PWID [55].

Numerous options to address adherence barriers have been considered in hopes of increasing PrEP efficacy and feasibility. PrEP *on-demand* would resolve the perceived burden of taking a pill daily and may be a more realistic approach for PWID. While PrEP *on-demand* has shown efficacy in reducing HIV transmission in other risk groups (e.g., MSM), it has not yet been tested in PWID [56]. Similarly, the National Institute of Health (NIH) is currently funding research on four types of long-acting PrEP [57], including an intravaginal ring, implant, injectable, and antibody infused. These forms of HIV prevention show the potential to reduce the incidence of HIV in high-risk populations but have not yet demonstrated efficacy. New biomedical techniques in HIV prevention will undoubtedly demand behavioral interventions to support their efficacy.

Limitations

Due to the synthesis of results, there is potential for publication bias in this systematic review. Also, we did not contact authors of the original articles to obtain disaggregated data on the PrEP care cascade in subgroups of PWID, nor did we contact researchers of ongoing studies to obtain relevant unpublished data. Other limitations include the lack of randomized controlled trials on PrEP uptake and adherence interventions among PWID. Only one study was found on an intervention increasing PrEP adherence in PWID; therefore, assumptions are limited in terms of efficacy. It is estimated that only 15% of high-risk individuals who

are eligible for PrEP achieve PrEP adherence [58, 59]. The scarcity of research in PWID contributes to the decrease in an engagement at each stage of the PrEP care cascade and demands future studies to address this gap.

Another limitation of the study is the ability to generalize across regions of the United States. To date, there has been a lack of representation of studies from the middle and southern United States, with only one study performed in rural West Virginia [26]. Research on the PrEP care cascade in PWID are quite limited, with studies only dating back to 2013 [13]. All reviewed studies were performed in a CBO, addiction treatment settings, SSP, or were part of the NHBS survey using self-reported measures.

Measurement methods varied across studies, reducing the internal validity of this review. Additionally, the characterization of the PrEP care cascade in PWID has been identified differently across researchers; while one research team identified “ability to access health care” as such [43], another research group identified this stage as “set an appointment with a doctor” [31]. Similarly, PrEP knowledge was defined differently across studies. Footer et al. (2019), for example, defined PrEP knowledge as knowing about the different PrEP modalities and side effects [20], Shrestha et al. defined PrEP knowledge as participants understanding the benefits of PrEP [29, 39], and McFarland et al. (2019) defined PrEP knowledge as the expression that PrEP can prevent HIV transmission through needle sharing. Although definitions vary, it is clear that the PrEP care cascade is synonymous across populations, such that PrEP eligibility, knowledge, and risk perception precede willingness to use PrEP, followed by access to HIV services and PrEP prescription and adherence/retention to PrEP care [31, 43, 58]. Definitions of the stages of the PrEP care cascade were condensed and recoded for data analysis.

Not all studies measured all six dependent variables of interest, thus producing some heterogeneity among cells. Specifically, PrEP awareness was measured by 18 studies [19–23, 26, 27, 31, 33–38, 40–43], PrEP knowledge [20, 27, 29, 39, 43] and HIV risk perception [20, 23, 32, 41, 42] were measured by five studies, willingness to use PrEP was measured by 14 studies [21–23, 26–28, 31, 34–36, 38, 40–42], access to HIV professionals was measured by 10 studies [19–22, 26, 28–31, 43], PrEP use was measured by 11 studies [22, 27, 30, 34, 37–43], and PrEP adherence was only measured by one study [30].

Conclusions

The use of PrEP in PWID has the potential to reduce HIV incidence by 10% in the United States [2]; however, PrEP use was reported in only 3% (n = 1/33) of participants across all studies we reviewed [22, 27]. Increasing access to PrEP in this at-risk group can help bridge the gaps in the PrEP care cascade. Participant characteristics in the studies included in this review can be used to inform future intervention design. Subgroups of PWID, including female sex workers and MSM, should be considered when tailoring and testing future interventions. Similarly, aspects of lower socioeconomic status and homelessness must be considered in maximizing the design of such interventions, including the optimal settings in which they should be implemented.

Barriers to use and access to HIV healthcare professionals are factors impeding PrEP uptake in PWID. Interventions for health care professions to increase self-efficacy in prescribing PrEP is an avenue for future research. A dramatic decrease from PrEP awareness to PrEP adherence demands implementation efforts that take into consideration the critical roles of health care professionals in settings where PWID seek treatment services. Despite study limitations, the current review points toward the need for improved evidence-based interventions for PrEP uptake, adherence, and persistence across the United States to significantly decrease HIV transmission among PWID.

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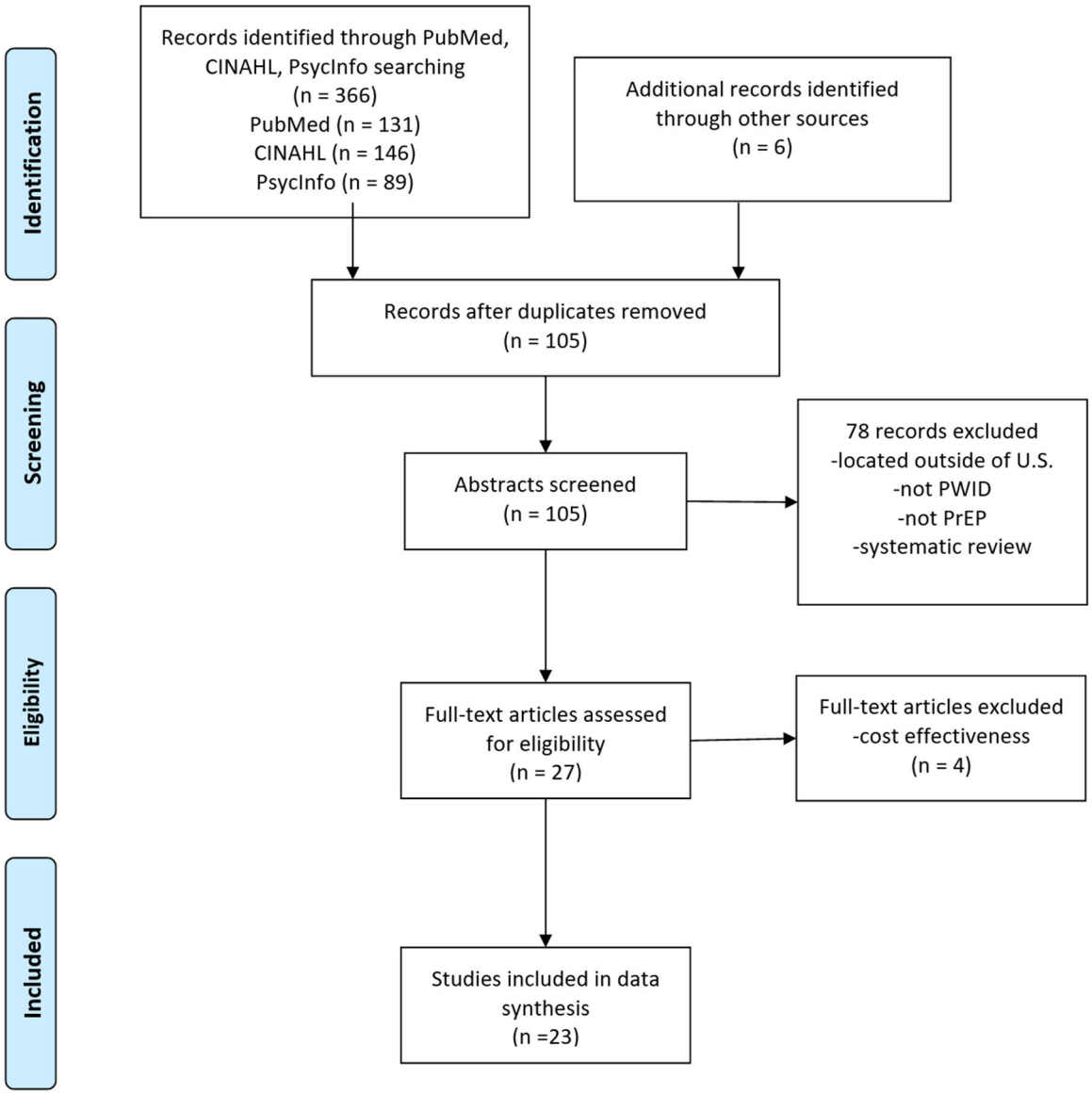

Figure 1.
PRISMA flow diagram

Table 1

Demographics and Overview of Studies

Study	Location	Participant characteristics	Study design / Recruitment	Key measurements / Variables
Allen et al., 2019 [26]	Kanawha County, West Virginia	N = 27 PWID Mean age = 38 years 59% male, 41% female 89% White, 3% Black N = 21 PWID Mean age = 37.3 years	Mixed Methods Qualitative semistructured interviews Quantitative Cross-Sectional Survey	PrEP Awareness Willingness to use Access to HIV Professional Barriers to use
	Cabell County, West Virginia	67% male, 33% female 95% White, 0% Black, 1% Mixed	CBO / HRP	
Bazzi et al., 2018 [27]	Boston, MA Providence, RI	N = 33 PWID Median age = 36 years 55% male, 45% female 67% White, 21% Black, 24% Hispanic/ Latinx 64% heterosexual, 36% LGBTQ	Qualitative SemiStructured Interview CBO / SSP / HIV testing center	PrEP Awareness PrEP Knowledge PrEP Use Barriers to use Willingness to use
Biello et al., 2018 [22]	Boston, MA Providence, RI	N = 33 PWID Median age = 36 years 55% male, 45% female 67% White, 21% Black, 24% Hispanic 64% heterosexual, 36% LGBTQ	Qualitative SemiStructured Interview CBO / SSP / HIV testing center	PrEP Awareness Willingness to use Barriers to use PrEP Use Access to HIV Professional
Felsher et al., 2020 [32]	Philadelphia, PA	N = 25 WWID Median age = 37 82% White, 9% Black, 9% Mixed race	Qualitative SemiStructured Interview HRP	Risk Perception Barriers to use
Footer et al., 2019 [20]	Baltimore, MD	N = 16 WWID Median age = 45 years 100% female 62% White, 38% Black 81% heterosexual, 19% LGBTQ	Qualitative Focus Groups SSP	PrEP Awareness PrEP Knowledge Barriers to use Risk Perception Access to HIV Professional
Jo et al., 2020 [31]	Miami, FL	N = 157 PWID Mean age = 39.7 (+/− 8.6) 74% male, 26% female 52% White, 3% Black, 39% Hispanic 90% heterosexual, 10% LGBTQ	Quantitative Cross-Sectional Survey SSP	PrEP awareness Willingness to use Barriers to use Access to HIV Professional
Kuo et al., 2016 [34]	Washington D.C.	N = 304 PWID Age = 17% >50 years, 83% <50 years 69% male, 31% female 2% Non-Black, 98% Black 84% heterosexual, 16% LGBTQ	Quantitative “Structured Behavioral Questionnaire” RDS sampling, NHBS	PrEP Awareness Willingness to use PrEP Use
Metz et al., 2017 [36]	New York City, NY	N = 138 OUD Mean age = 46.5 years 83% male, 17% female 89% heterosexual, 11% LGBTQ	Quantitative Cross-Sectional Survey Substance Use Research Center	PrEP Awareness Willingness to use
McFarland et al., 2019 [43]	San Francisco, CA	N = 398 PWID 82% heterosexual, 18% MSM	Quantitative “Structured Behavioral Questionnaire” RDS sampling, NHBS	PrEP Awareness PrEP Knowledge PrEP Use Access to HIV Professional
Peitzmeier et al., 2017 [21]	Baltimore, MD	N = 60 FSW, 87% reported IDU in past 90 days Mean age = 35.5 years 100% female 72% White, 16% Black	Quantitative Cross-Sectional CBO / SSP / sexual health services	PrEP Awareness Willingness to use Barriers to use Access to HIV Professional
Roth et al., 2018 [28]	Camden, NJ	N = 138 PWID Median = 32 years 53% male, 47 % female 73 % White, 15% Black,	Quantitative Cross-Sectional Survey Mobile SSP	Willingness to use Barriers to use Access to HIV Professional

Study	Location	Participant characteristics	Study design / Recruitment	Key measurements / Variables
		5% Hispanic, 2% other 79% heterosexual, 21% LGBTQ		
Roth et al., 2019 [37]	Philadelphia, PA	N = 612 PWID Mean age = 30–39 years 75% male, 25% female 68% White, 11% Black, 19% Hispanic/ Latinx, 2% other 86% heterosexual, 14% LGBTQ	Quantitative “Structured Behavioral Questionnaire” RDS sampling, NHBS	PrEP Awareness PrEP Use Access to HIV Professional
Sherman et al., 2019 [35]	Baltimore, MD	N = 265 PWID Mean age = 45 years 68% male, 32% female %55% Black, 40% White, 5% other 92% heterosexual, 8% LGBTQ	Quantitative Cross-Sectional Survey SSP	PrEP Awareness Willingness to use
Shrestha & Copenhaver 2018 [30]	New Haven, CT	40 Methadone maintained individuals on PrEP Mean age = 44.8 years (+/−11.8) 55% male, 45% female 58% White, 33% Black, 7% Latinx, 2% other 78% heterosexual, 22% LQBTQ	Mixed Methods Qualitative semistructured interviews Quantitative Cross-Sectional Survey MMP	Barriers to use PrEP Use Access to HIV Professional
Shrestha et al., 2017 [38]	New Haven, CT	N = 400 Methadone maintained individuals Mean age = 40.9 years 59% male, 41% female 63% White, 18% Black, 15% Hispanic, 4% other 86% heterosexual, 14% LGBTQ	Quantitative Cross-Sectional Survey MMP	PrEP Awareness Willingness to use PrEP Use
Shrestha et al., 2017 [29]	New Haven, CT	N = 20 Methadone maintained individuals Mean age = 42 years 45% male, 55% female 65% White, 25% Black, 10% other	Qualitative Focus Groups MMP	PrEP Knowledge PrEP Awareness Barriers to use
Shrestha et al., 2017 [41]	New Haven, CT	N = 400 Methadone maintained individuals Mean age = 40.9 years 59% male, 41% female 63% White, 18% Black, 15% Hispanic, 4% other 86% heterosexual, 14% LGBTQ	Quantitative Cross-Sectional Survey MMP	PrEP Awareness Willingness to use PrEP Use Risk Perception
Shrestha et al., 2017 [42]	New Haven, CT	N = 400 Methadone maintained individuals Mean age = 40.9 years 59% male, 41% female 63% White, 18% Black, 15% Hispanic, 4% other 86% heterosexual, 14% LGBTQ	Quantitative Cross-Sectional Survey MMP	PrEP Awareness Willingness to use PrEP Use Risk Perception
Shrestha et al., 2018 [39]	New Haven, CT	40 Methadone maintained individuals on PrEP Mean = 44.8 years 55% male, 45% female 58% White, 33% Black, 7% Latinx, 2 % other 78% heterosexual, 22% LGBTQ	Mixed Methods Qualitative semistructured interviews Quantitative Cross-Sectional Survey MMP	PrEP Knowledge PrEP use
Shrestha et al., 2018 [40]	New Haven, CT	N = 400 Methadone maintained individuals Mean age = 40.9 years 59% male, 41% female 63% White, 18% Black, 15% Hispanic, 4% other 86% heterosexual, 14% LGBTQ	Quantitative Cross-Sectional Survey MMP	PrEP Awareness Willingness to use PrEP Use
Stein et al., 2014 [23]	Fall River, MA	N = 351 PWID Mean = 32.3 years 70% male, 30% female 86% White, 3% Black, 8% Hispanic, 3% other	RCT, Quantitative Cross-Sectional Survey Addiction Treatment Center	PrEP Awareness Willingness to use Barriers to use Risk Perception
Walters et al., 2017a [33]	New York City, NY	N = 118 WWID Mean age = 45 years, 40% 50+ years 100% women 38% Latinx, 37% Black, 25% White	Quantitative “Structured Behavioral Questionnaire” RDS sampling, NHBS	PrEP Awareness

Study	Location	Participant characteristics	Study design / Recruitment	Key measurements / Variables
Walters et al., 2017b [19]	New York City, NY	N = 468 PWID, 486 MSM Mean age = 45 years 74% male, 25% female	Quantitative "Structured Behavioral Questionnaire" RDS sampling, NHBS	PrEP Awareness Access to HIV Professional
	Long Island, NY	N = 196 PWID, 307 MSM Mean age = 45 years 68% male, 32% female		

PrEP Pre-Exposure Prophylaxis, PWID People who inject drugs, CBO Community-Based Organization, HRP Harm Reduction Program, SSP Syringe Services Program, MMP Methadone Maintenance Program, RDS Response driven sampling, NHBS National HIV Behavioral Surveillance

Table 2

PrEP Care Cascade in PWID

Study	PrEP Awareness	Prep Knowledge	Willingness to use	Risk Perception	Barriers to PrEP Use	Access to HIV Professional	PrEP Use
Allen et al., 2019 [26]	33% aware of PrEP		65% interested in taking PrEP		*cost, access to health care, homelessness, adherence adherence facilitators Social support	*suggested HIV services at SSP	
Bazzi et al., 2018 [27]	36% heard of PrEP	*low accuracy in PrEP knowledge	unlikely= 9%, undecided= 39%, likely= 30%, extremely likely=21% *low willingness HIV risk perception, do not share needles, not a priority high willingness HIV risk perception, sex workers, sharing syringes, know PLWH		*health care provider stigma		3% on PrEP
Biello et al., 2018 [22]	36% heard of PrEP		extremely unlikely = 0, unlikely = 9%, undecided = 39%, likely = 30%, extremely likely =21% *more willing with appropriate supports		*knowledge, HIV risk perception, side effects, health priorities, chaotic lifestyle, poor infrastructure, health care provider stigma, homelessness, criminal justice system, cost, HIV stigma within social networks	*suggested CBO as ideal environment for PrEP delivery identified positive relationships with CBO/SSP staff	3% on PrEP
Felsher et al., 2020 [32]				48% perceived themselves to be at risk for HIV	*medicine interactions, PrEP and HIV related stigma, access to health care		
Footer et al., 2019 [20]	31% heard of PrEP	13% knew PrEP knowledge		“how often do you worry about HIV?” never =18.7%, some of the time = 18.7%, moderate amount of time = 6.4%, most of the time=	*family/partner stigma, access to health care, medicine interactions, adherence, side effects, homelessness	*suggested integrating PrEP promotion in MMP	
Jo et al., 2020 [31]	28.3% heard of PrEP		23% willing to use PrEP opioid injection (compared to polysubstance	52% lack of knowledge, 39.5% cost	5.7% requested appointments with a PrEP provider		

Study	PrEP Awareness	Prep Knowledge	Willingness to use	Risk Perception	Barriers to PrEP Use	Access to HIV Professional	PrEP Use
			injection) had decreased odds of willingness to use				
Kuo et al., 2016 [34]	13.4% heard of PrEP		if PrEP were free: 47.2% likely 23.5% somewhat likely 29.3% not likely characteristics associated with willingness to use: bisexual, screening positive for depressive symptoms, having two or more sex partners in the past 12 months, injection cocaine use, being >50 years old, and sharing drug paraphernalia		0% on PrEP		
Metz et al., 2017 [36]	30% heard of PrEP, no sig. difference between ethnic groups		39% yes 20% probably				
McFarland et al., 2019 [43]	57% heard of PrEP, women more likely than men	39% knew PrEP knowledge		MSM were more likely to have discussed PrEP with a healthcare provider than non-MSM PWID	3% on PrEP, all identifying as MSM, females more likely than straight males to have used PrEP		
Peitzmeier et al., 2017 [21]	33% aware of PrEP	43% very interested, 17% somewhat interested, 4% somewhat disinterested, 21% very disinterested <35 years more interested than if >35 years	adherence	*successful recruitment at mobile health clinics providing HIV testing and needle exchange			
Roth et al., 2018 [28]		79.3% willing to use PrEP, females were more willing to use, more likely to report a willingness to tolerate adverse effects of PrEP, and quarterly HIV testing than males	51.6% anxiousness 45% embarrassed 51.4% did not want a partner to know	73.2% preferred HIV testing from a mobile van			
Roth et al., 2019 [37]	12.4% aware of PrEP			18.4% discussed	2.6% on PrEP		

Study	PrEP Awareness	Prep Knowledge	Willingness to use	Risk Perception	Barriers to PrEP Use	Access to HIV Professional	PrEP Use
	sig. more aware groups female, sexual minority, college education, attending CBO, past STI testing, sharing drug paraphernalia, and use of SSP			PrEP w healthcare provider *participants recommend utilizing SSP for increasing PrEP awareness			
Sherman et al., 2019 [35]	24% aware of PrEP	63% somewhat or very interested characteristics associated with willingness to use: homeless, being PrEP eligible, and having other medical diagnoses					
Shrestha & Copenhaver 2018 [30]					*long-term side effects, stigma, adherence, access to health care adherence facilitators use of memory aid, (lack of) cost with insurance, perceived benefit, social support	55% were prescribed PrEP from a substance abuse treatment clinic, 14% from community health care van	100% on PrEP adherence score of 87.6 (+/− 18.6)
Shrestha et al., 2017 [38]	18% aware of PrEP		63% willing to initiate PrEP IMB determinants in willingness to use PrEP information predicted behavioral skills, motivation predicted behavioral skills, behavioral skills predicted willingness to use PrEP				1.8% on PrEP
Shrestha et al., 2017 [29]	5% heard of PrEP	*knowledge of high-risk individuals and HIV prevention			*cost, side effects, medication interactions		
Shrestha et al., 2017 [41]	18% aware of PrEP		63% willing to initiate PrEP characteristics associated with willingness to use: NCI and higher perceived HIV risk	66% at risk of acquiring HIV			1.8% on PrEP
Shrestha et al., 2017 [42]	18% aware of PrEP		63% willing to initiate PrEP characteristics associated with	66% at risk of acquiring HIV			1.8% on PrEP

Study	PrEP Awareness	Prep Knowledge	Willingness to use	Risk Perception	Barriers to PrEP Use	Access to HIV Professional	PrEP Use
			willingness to use: NCI and HIV risk behavior NCI was also associated with HIV risk behavior				
Shrestha et al., 2018 [39]		increase in PrEP related knowledge					100% on PrEP increase in adherence post intervention
Shrestha et al., 2018 [40]	18% aware of PrEP		mean willingness of 56.2%				1.8% on PrEP
Stein et al., 2014 [23]	7.4% heard of PrEP		Group 1 58.2% willing Group 2 47.1% willing *High willingness perceived risk of HIV	54.9% at some risk, 39.1% low risk, 11.7% average risk, 2.9% moderate risk, 1.1% very high risk	*cost, adherence, risk compensation, stigma, blood tests, STI risk, access to health care		
Walters et al., 2017a [33]	1% heard of PrEP, increased PrEP awareness if used SSP and reported transactional sex						
Walters et al., 2017b [19]	21% of PWID in NYC aware of PrEP, 15% of PWID in L.I. aware of PrEP Decreased odds for awareness if: male or female compared to MSM. Increased odds for awareness if exposure to health professionals, HIV+, reported cocaine and heroin use, and greater household income					New York 25% of WWID and 24% of males who inject drugs reported access to HIV prevention professionals New Jersey 36% PWID reported access to HIV prevention professionals	

*qualitative themes