SUBSTANTIVE REVIEW

Suboptimal HIV Pre-exposure Prophylaxis Awareness and Willingness to Use Among Women Who Use Drugs in the United States: A Systematic Review and Meta-analysis

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Abstract

In the United States (U.S.), more than 12 million women reported illicit drug use in the past month. Drug use has been linked to increased risk for HIV, but little is known about the uptake of HIV pre-exposure prophylaxis (PrEP) to prevent HIV among women who use drugs (WWUD). Following the PRISMA guideline, we conducted a multi-database literature search to assess engagement along the PrEP care continuum among WWUD in the U.S. Seven studies with a total of 755 women were included in the review: 370 (49%) Black, 126 (16.7%) Hispanics, and 259 (34.3%) Whites. Employing random-effect models, data indicate 20.6% (95% CI 8.7%, 32.4%) of WWUD were aware of PrEP, and 60.2% (95% CI 52.2%, 68.2%) of those aware were also willing to use PrEP. Notwithstanding study limitations, our findings suggest there may be potential to increase PrEP uptake among WWUD, but efforts must first concentrate on improving PrEP awareness among this population.

Keywords Women who use drugs · Pre-exposure prophylaxis · Systematic review · Meta-analysis · United States

Resumen

En los Estados Unidos (EE. UU.), más de 12 millones de mujeres reportaron el uso de drogas ilícitas en el último mes. El uso de drogas se ha relacionado con un mayor riesgo de contraer el VIH, pero se sabe poco sobre la aceptación de la profilaxis preexposición (PrEP) para prevenir el VIH entre las mujeres que consumen drogas (MQCD). Siguiendo la guía de PRISMA, realizamos una búsqueda bibliográfica en múltiples bases de datos para evaluar el compromiso a lo largo de la cascada de atención de PrEP entre MQCD en los EE. UU. Se incluyeron siete estudios con un total de 755 mujeres en la revisión: 370 (49%) afroamericanas, 126 (16,7%) hispanas y 259 (34,3%) blancas. Empleando modelos de efectos aleatorios, los datos indican que el 20,6% (IC 95% = 8,7%, 32,4%) de MQCD tenían conocimiento de la PrEP, y un impresionante 60,2% (IC 95% = 52,2%, 68,2%) de las informadas también estaban dispuestas a utilizer la PrEP. A pesar de las limitaciones del estudio, nuestros hallazgos sugieren que puede haber un potencial para aumentar la aceptación de PrEP entre MQCD, pero los esfuerzos deben concentrarse primero en mejorar la conciencia de PrEP entre esta población.

Palabras clave Mujeres que usan drogas · Profilaxis preexposición · Revisión sistemática · Metanálisis · Estados Unidos

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Introduction

By 2013, women accounted for almost half of all 24.6 million people who reported past-month illicit drug use in the United States [1]. Of the HIV diagnoses attributed to injection drug use, more than 40% were among women [2]. Women who use drugs (WWUD) are at elevated risk for HIV acquisition [2] for various reasons, such as, receptive syringe sharing and drug-influenced disinhibited sexual risk behaviors, as well as by the high prevalence of transactional sex and syndemic risk factors observed in this population (violence, poverty, disempowerment and lack of care access) [3–5] One study conducted in 20 United States (U.S.) cities indicated that two-fifths of 2305 women who inject drugs reported selling sex for money, goods or drugs at least once in the past year, with the majority of sex exchange encounters involving condomless sex [6]. An immediate and effective tool is urgently needed to supplement behavioral prevention approaches (e.g., condom use, syringe exchange) to prevent HIV acquisition and transmission among WWUD [7–11].

Pre-exposure prophylaxis (PrEP) via once daily oral administration of Truvada (emtricitabine/tenofovir disoproxil fumarate), a U.S. Food and Drug Administration (FDA)-approved HIV anti-retroviral medication, has been shown to be highly efficacious in reducing HIV incidence among high-risk populations [12–15]. However, the benefits of PrEP remain largely unrealized in real-world settings due to various individual and contextual barriers across the PrEP care continuum (i.e., PrEP awareness, willingness to use PrEP, linkage to PrEP care, PrEP uptake, retention, and adherence) [16, 17]. As the entry stage to the PrEP care continuum, PrEP awareness/willingness to use is essential; no further actions can be taken to achieve sustained PrEP adherence and risk reduction benefits unless this stage has been achieved. Recent studies have revealed a moderate level of PrEP awareness or willingness to use among several key populations, including men who have sex with men (MSM) and sero-discordant couples [18–22].

Furthermore, Choopanya et al. [12] conducted a clinical trial to assess the efficacy of PrEP among Thai men and women who inject drugs (PWID), and found significantly lower HIV incidence among those taking daily Truvada (0.35 vs. 0.68 per 100 person-year), with showing more effective among women as they had lower incidence compared to men in the treatment group (0.20 vs. 0.39 per 100 person-year). Despite the demonstrated efficacy of PrEP among PWID and the elevated risk of HIV acquisition among WWUD, few studies have assessed the implementation of PrEP in this group or explored the challenges/opportunities across the PrEP care continuum to inform future prevention intervention efforts among WWUD [23]. Although no studies

have revealed the proportion of WWUD who are currently using PrEP, limited PrEP research involving WWUD in the U.S has revealed that participants have been highly satisfied with PrEP and considered PrEP as an essential tool for HIV prevention [24]. PrEP recipients have reported no adverse impact on quality of life as a result of taking PrEP [25], and other participants would accept PrEP with caution [26]. In spite of these limited observations, characterization of the key stages of the PrEP care continuum among WWUD remains poorly understood in the U.S.

Following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline (http://www.prisma-statement.org/), we gathered evidence from published studies and meta-analytically described key stages along the PrEP continuum among WWUD in the U.S., including all available studies with rigorous study designs. This systematic review and meta-analysis is meant to provide empirical guidance for future targeted PrEP programs and interventions among this particularly high-risk group.

Methods

Eligibility Criteria

Inclusion Criteria

Published articles were included if they: (a) sampled women or reported data separately for women and men who reported either injection or non-injection illicit drug use (e.g., marijuana, cocaine, heroin, methamphetamine, hallucinogens); (b) used quantitative inferential study designs (e.g., randomized control trials, cross-sectional/cohort studies); (c) reported quantitative measures (e.g., proportion) on any stage of the PrEP care continuum (i.e., PrEP awareness, acceptance/willingness to use PrEP, PrEP uptake/use) or provided sufficient information to calculate pooled estimates; (d) were peer-reviewed and published in English between January 1, 2012 until July 5, 2018; and (e) can be searched from indexed databases or published sources. Our search start date parameter was selected to coincide with U.S. FDA approval of PrEP for HIV prevention among individuals aged 18 or older [27].

Exclusion Criteria

The exclusion criteria included: (a) descriptive studies (e.g., case reports) or qualitative studies without quantitative measurement; (b) studies that did not report results for a segregated subgroup of WWUD (e.g., a mixed sampling of people who use drugs and people who do not use drugs); (c) reviews/meta-analysis; and (d) theoretical/modeling studies without original data.

Information Sources, Search and Study Selection

Following the PRISMA guidelines, we conducted a comprehensive literature search of the following databases: PubMed/MEDLINE, Web of Science, PsycINFO, EMBASE, and GOOGLE SCHOLAR. Our Boolean search queries were: ("HIV" OR "human immunodeficiency virus" OR "AIDS" OR "acquired immunodeficiency syndrome") AND ("PrEP" OR "pre-exposure prophylaxis") AND ("woman (women)" OR "female(s)" OR "girl(s)") AND ("drug use" OR "drug-using" OR "drug abuse" OR "drug dependence" OR "substance abuse" OR "substance dependence"). We also searched through conference proceedings, as well as references from articles/reviews that met our inclusion criteria. Two reviewers (CZ and YL) independently reviewed articles identified in the initial search. The interrater reliability was > 90%, and disagreement between reviewers was resolved by discussion.

Data Collection and Quality of Evidence Assessment

Two reviewers independently extracted data from eligible articles using a standardized form to record the following information: (a) location and year of the study conducted, (b) demographic characteristics of participants (e.g., age, race/ethnicity), (c) sample size, (d) study design, (e) recruitment strategy, (f) key measurements (e.g., PrEP awareness and willingness to use), and (g) key findings and notes or other informative features. For studies with duplicate publications [28, 29], we reported the study only once in the analyses, with the most complete data included. Three studies reported PrEP awareness [30–32], and six studies reported willingness to use PrEP [28–33] specifically among WWUD. In addition, we employed the GRADE rating scheme to evaluate the quality of evidence from each individual study using recommended criteria (i.e. risk of bias, precision, consistency, directness) [34].

Statistical Analysis

Measures

Prevalence of *PrEP awareness* (i.e. proportion of those who had ever heard of PrEP among all interviewed WWUD) and *willingness to use PrEP* (i.e. proportion of those who self-reported willingness to take PrEP among all interviewed WWUD) were the key measures in the current analysis.

Assessment of Heterogeneity and Publication Bias

We used the I^2-*statistic* and corresponding 95% confidence intervals (CI) to depict heterogeneity. The I^2-*statistic* describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error, with higher percentages indicating higher heterogeneity [35, 36]. Heterogeneity statistic (i.e., tau-squared) and its corresponding *p* value were also reported for each analysis. Publication bias was assessed by funnel plots and Egger's test [37]. Funnel plots were employed to visually assess the asymmetry, while Egger's test was used to test the asymmetry statistically.

Data Synthesis, Subgroup and Sensitivity Analyses

We employed the DerSimonian-Laird random-effects model to weight and pool the individual estimates [38], as all included studies were conducted among populations across heterogeneous settings [35]. Unlike the fixed effects model that assumed all studies shared identical true effect sizes, the random effects model was designed to capture variances of estimates across studies [35, 39]. Forest plots were used to illustrate the aggregate findings. We also performed subgroup analyses to examine the pooled estimates if the pooled estimates differed by sample (e.g., women who use drugs vs. women who inject drugs only, men and women [mixed] who use drugs vs. men and women (mixed) who inject only) because drug use behavior may correlate with HIV risk and PrEP utilization. Sensitivity analyses were employed to examine the stability of the pooled estimates by evaluating whether the overall pooled estimates were sensitive to exclusion of any individual studies (e.g., study with highest or lowest weight, studies with lowest rating, and with smallest or largest sample size). We performed all statistical and meta-analysis using STATA 15 (College Station, TX). The STATA *Metaprop* command was used to pool the data as it was particularly designed for binomial data, using the binomial distribution to model within-study variances [40]. Based upon this strategy, the Method of Moments is used to estimate the mean, but Maximum Likelihood is used to estimate heterogeneity. [38, 40] The *Metaprop* command computes 95% CI using the score statistics (for smaller sample size) that allows incorporation of the Freeman-Tukey double arcsine transformation [41] of proportion to generate admissible pooled estimates within the range of [0, 1], which has been validated by multiple studies [40, 42, 43].

Narrative Synthesis

In order to identify factors that may affect PrEP use among WWUD, we employed a narrative synthesis approach to identify predisposing (e.g., patient-level factors) and enabling factors (e.g., available resources that may facilitate PrEP use) as well as needs components (e.g., health status barriers, belief or perceptions) based upon the *Behavioral Model of Healthcare Utilization for Vulnerable Populations* [23, 44].

Results

Study Selection, Characteristics, and Risk of Biases Across Studies

Our initial search yielded 203 citations. After title/abstract screening, 109 references were full-text reviewed, with seven studies meeting all inclusion criteria (Fig. S1). Among these publications, findings from one abstract [28] overlapped with another article [29], and two articles reported findings from the same study [33, 45]. Another study reported separate information for women who inject drugs in New York City and Long Island, and we treated these two data points separately [32]. A total of eight articles and one abstract, reporting findings from seven individual studies, were retained after rigorous selection.

Details about each included study are presented in Table 1. We pooled the numbers of WWUD from all selected studies. Our pooled sample size is 755, including 370 Black (49%), 126 Hispanic (16.7%), and 259 (34.3%) White women. All studies used cross-sectional designs; three were conducted in New York [31, 32, 46], and one each in Maryland [30], Washington DC [28, 29], Connecticut [33, 45], and Massachusetts [47]. Three studies (reported by three articles and one abstract) were secondary data analyses of the National HIV Behavioral Surveillance (NHBS) data [28, 29, 31, 32]. Four studies used convenience sampling to recruit participants from health services settings, including syringe exchange and sexual health services [30], opioid detoxification programs [47], or methadone maintenance programs [33, 45]. Among the included studies, six reported prevalence of PrEP awareness [28, 30–33, 45, 46] with three reporting women-specific data; [30–32] four reporting prevalence of PrEP use willingness and all four reporting women-specific information [30, 33, 47]. Most studies used self-reported HIV status [28, 29, 31–33, 45–47], and some studies did not report ethnicity/race specific data in relation to PrEP use [28, 29, 31–33, 45–47].

PrEP was usually referred to as "a pill to prevent HIV" in these included studies. In most studies, PrEP awareness was assessed by a single question, such as *"HIV Pre-exposure prophylaxis, or PrEP, is a way for people who do not have HIV to prevent HIV infection by taking a pill every day?";* or *"Have you heard of HIV PrEP before today?"*; or *"Before today, have you ever heard of people who do not have HIV taking antiretroviral medicines, to keep from getting HIV?"* [28–33, 45–47]. For willingness to use PrEP, all studies assessed participants' willingness by asking general questions, such as "*If a daily HIV pill to prevent you from getting HIV was available in DC for free or was covered by your health insurance, how likely would you be to take it?*", or "*How interested would you be in*

taking a pill every day to prevent HIV infection?" [28, 29]. One study assessed participants' willingness to take PrEP using specific risk reduction information (i.e., *"Would you be willing to take a once a day pill every day to lower your risk 90% (or 40%) of becoming HIV positive?"*) [47]. In addition to these two key measures (awareness and willingness to use), several studies also reported participants' perception of potential risk compensation (PrEP users may conduct more risky behaviors as they feel protected by taking PrEP). Questions assessing risk compensation included *"I will no longer need to sterilize or use clean needles/use condoms or practice safe sex if I am taking pills to prevent HIV infection"* or *"Would you take PrEP if you still had to use condoms to be fully protected from HIV?"* [28–30, 33, 45, 47].

Synthesis of Results

In studies that involved WWUD samples, the pooled prevalence of PrEP awareness was 20.6% (95% CI 8.7%, 32.4%). However, once these participants were informed of PrEP, willingness of PrEP use was 60.2% (95% CI 55.2%, 64.1%) among injectors and non-injectors and 57.3% (95% CI 48.8%, 65.9%) among injectors only, respectively. Very few women reported PrEP uptake (i.e., ever taking PrEP) across included studies [31, 33, 45]. For example, in the study by Walters et al. (2017), < 1% of injectors (1 of 118) reported ever using PrEP [31]. In another study involving mixed men and women who use drugs, only 1.8% ever used PrEP [33, 45]. No data for PrEP care retention and adherence were reported in any included studies (Figs. S2, S3). In addition to measurements of the PrEP cascade, four studies reported respondents' perception of potential risk compensation under the hypothetical scenario of initiating PrEP (Table 2) [28–30, 33, 45, 47]. The pooled proportion of perceived risk compensation among all men and women (mixed) who use drugs was 26.1% (95% CI 6.9%, 45.2%), and among men and women (mixed) who inject drugs was only 18.4% (95% CI 9.9%, 26.8%). No gender-specific data regarding risk compensation perceptions were available (Table 2; Fig. 1, Fig. S6).

Risk of Biases Within and Across Studies

The quality of evidence for most outcomes was scored as low or very low, primarily due to the nature of observational study design, limited sample size, and generalizability (Table 1). Publication bias was assessed by funnel plot, where the standard error of the effect size was plotted against the effect size. Examining the funnel plot revealed that publication bias was present, as the graph showed slight asymmetry within the funnel (Figs. S4, S5, S7). We were

Table 1 Summary of included studies for drug-using women (n = 7 studies)

Authors/Year of publication	Location and time	Recruitment	Characteristics of participants	Study design	Key measurements	Key findings	[a]GRADE rating	Notes
Levin (2014), Kuo (2016)	Washington, DC (2012)	IDUs were recruited using RDS from NHBS 2012 system and completed a detailed behavioral quantitative interview and underwent rapid testing for HIV	HIV-negative IDUs, n = 304 (203 males, 98 females) and 82.7% were 50 years or older, Black = 97.2%	Cross sectional; quantitative	*Willingness of PrEP use* (e.g., "If a daily HIV pill to prevent you from getting HIV was available in DC for free or was covered by your health insurance, how likely would you be to take it?")	Only 13.4% had ever heard of using anti-HIV medication to prevent HIV; none had ever used PrEP or knew anyone who used it in the past year. Forty-seven percent were very likely and 24% were somewhat likely to take PrEP if it were available without cost; 13% agreed they would not need to sterilize/clean needles or use condoms if taking PrEP. None had ever taken PrEP.	⊕⊕OO Observational study design with limited representativeness; risk of bias is low or unclear	Mixed men and women; IDU only; no racial specific analyses; hypothetical scenario; self-reported HIV negative
Metz (2017)	NYC (2014–2015)	Participants had responded to local flyer or newspaper advertisements for non-treatment-seeking adults with opioid use disorders who would like to participate in a clinical research study. The current study was conducted at the substance use research center	138 adults with opioid use disorder (24 female, 114 male; mean age = 46.5 years (SD = 9.5); Black = 46.3%, White = 24.6%, Hispanic = 24.6%	Cross sectional; quantitative	*PrEP awareness* Participants were asked about chemical prevention, Truvada, and PrEP	29% of all participants heard of Truvada, and 30% heard of PrEP. White opioid users showed the most risk behaviors among races/ethnicities, despite comparable prevention knowledge. 3 HIV positive among women (3/24 = 13%), 30% women are IDU	⊕OOO Observational study design with a very small sample size; risk of bias is low or unclear	Mixed men and women; mixed types of drug users, no gender specific data available; hypothetical scenario; urine toxicology for drug dependency; self-reported HIV status

Table 1 (continued)

Authors/Year of publication	Location and time	Recruitment	Characteristics of participants	Study design	Key measurements	Key findings	[a]GRADE rating	Notes
Peitzmeier (2017)	Baltimore, MD (2015)	Participants were recruited from two sites of a mobile health service that provides needle exchange and sexual/reproductive health services in Baltimore, Maryland	Female sex workers, n = 60, mean age = 35.5 years, Black = 16%, White = 72%, IDU = 90%	Cross sectional; quantitative	*PrEP awareness* (e.g., "HIV pre-exposure prophylaxis, or PrEP, is a way for people who do not have HIV to prevent HIV infection by taking a pill every day. Have you heard of HIV PrEP before today"); *Willingness of PrEP use* (e.g., "How interested would you be in taking a pill every day to prevent HIV infection")	33% heard of PrEP; 65% were interested in taking PrEP; Self-efficacy for daily oral adherence (79%); 78% were still interested in using PrEP even if condoms were still necessary; potential risk compensation (22%)	⊕OOO Observational study design with a small sample size; risk of bias is low or unclear	Women only; 90% IDU; no racial-specific analyses; hypothetical scenario; no assessment of HIV status
Shrestha (2016, 2017)	Connecticut (2016)	A convenience sample of 400 participants was recruited at Connecticut's largest MMP; ACASI-based survey	400 HIV-negative, opioid dependent participants (234 males and 166 females); mean age = 40.9 years (SD = 11.1); non-White = 36.8%, White = 63.2%	Cross sectional; quantitative	*PrEP Awareness* (yes vs. no); *Willingness of PrEP use* (e.g., "I would be interested in taking PrEP to reduce my current risk of HIV infection" on a five-point Likert scale)	While only 72 (18%) were aware of PrEP, after being given a description of it, 251 (62.7%) were willing to initiate PrEP. Among those willing to initiate PrEP, only 12.5% and 28.2%, respectively, indicated that they would always use condoms and not share injection equipment while on PrEP. 1.8% of participants ever used PrEP	⊕⊕OO Observational study design with indirect measurement of willingness; risk of bias is low or unclear	Mixed men and women; mixed types of drug users, hypothetical scenario; self-reported HIV negative

Table 1 (continued)

Authors/Year of publication	Location and time	Recruitment	Characteristics of participants	Study design	Key measurements	Key findings	[a]GRADE rating	Notes
Stein (2014)	Massachusetts (2013)	Consecutive persons seeking opioid detoxification were approached at the time of admission to Stanley street treatment addiction and recovery in fall river, Massachusetts to participate in a survey research study.	351 opiate injectors entering detoxification treatment (105 female opiate injectors, 246 males), 87% non-Hispanic White; mean age=32.2 years (SD=10.1)	Cross sectional; quantitative	*PrEP awareness* (e.g., "Have you heard of a pill that is safe and effective in lowering transmission of HIV?"); *Willingness of PrEP use* (e.g., "Would you be willing to take a once a day pill every day to lower your risk 90% (or 40%) of becoming HIV positive?")	Only 7.4% had heard of a drug to reduce HIV risk, yet once informed, 47.1% would be willing to take such a pill [35% of those in the low effectiveness scenario and 58% in the high group (p<.001)]; perceived no risk of HIV (45.1%) and perceive barriers of PrEP use	⊕⊕OO Observational study design with inconsistent measurement of willingness; risk of bias is low or unclear	Mixed men and women; IDUs only, no race specific analyses; hypothetical scenario. Toxicologically confirmed; self-reported HIV status
Walter 2017-NYC	NYC (2011–2013)	NHBS2012 system was conducted in 20 cities. Data for this analysis was from the NYC, and RDS was used; face-to-face interviews	122 female IDUs: 29% were 50 years or older; Black=25%, Hispanic=52%, White=22%	Cross sectional; quantitative	*PrEP Awareness* (e.g., "Before today, have you ever heard of people who do not have HIV taking antiretroviral medicines, to keep from getting HIV?"	Female IDU had 52% of decreased odds of PrEP awareness compared to MSM. Only 12% female IDU reported PrEP awareness; 14% (n=17) were HIV positive	⊕⊕OO Observational study design with limited representativeness; risk of bias is low or unclear	IDU only; no racial-specific analyses; hypothetical scenario; women-specific data available; self-reported HIV status
Walter 2017-Long Island	Long Island (2011–2013)	Data for this analysis was from the Nassau-Suffolk, NY (i.e., Long Island), part of the NHBS using RDS; face-to-face interviews	63 female IDUs: 25% were 50 years or older; Black=56%, Hispanic=8%, White=37%			Female IDU had 82% of decreased odds of PrEP awareness compared to MSM. Only 8% female IDU reported PrEP awareness; 6% (n=4) were HIV positive		

Table 1 (continued)

Authors/Year of publication	Location and time	Recruitment	Characteristics of participants	Study design	Key measurements	Key findings	aGRADE rating	Notes
Walters (2017)	NYC (2015)	2015 National HIV Behavioral Surveillance (NHBS 2015) system cycle on injection drug use collected in New York City (NYC) using RDS	118 women who inject drugs were included, 40% were 50 years or older; Latina = 38%, Black = 37%, White = 25%; (74%) reported previous incarcerated in their lifetime	Cross sectional; quantitative	*PrEP awareness* (e.g., Before today, have you ever heard of people who do not have HIV taking PrEP, the antiretroviral medicine taken every day for months or years to reduce the risk of getting HIV?)	Awareness of PrEP was relatively low (31%), and only 1 WWID reported taking PrEP.	⊕⊕OO Observational study design with wide confidence intervals; risk of bias is low or unclear	WWID only, no race-specific analyses; hypothetical scenario; self-reported HIV negative

PrEP pre-exposure prophylaxis, *IDU* injecting drug users, *RDS* respondent-driven sampling, *NHBS* National HIV Behavioral Surveillance, *NYC* New York city, *MMP* methadone maintenance program, *SD* standard deviation, *ACASI* audio computer-assisted self-interviewing, *WWID* women who inject drugs

aGRADE rating for quality of evidence: ⊕OOO-very low quality; ⊕⊕OO-low quality

unable to conduct further tests on the funnel plot asymmetry, as there were fewer than ten studies included and the power was too low to distinguish chance from statistically significant asymmetry [37, 48]. We further examined the heterogeneity using I^2-statistic (ranged from 50.8 to 91.7%) across different subgroup analyses; this indicated moderate to high heterogeneity of the studies. *p*-values of heterogeneity Chi squares also indicated significant heterogeneity across included studies (Table 2).

Additional Analyses

Sensitivity analyses were conducted by removing studies with highest and lowest weight, studies with largest and smallest sample size, and studies rated as "very low" by GRADE scoring scheme, respectively. Comparing outcomes from sensitivity analyses with the original outcome, no difference was found from the original sensitivity analyses (not shown).

From the narrative analysis, predisposing factors of PrEP willingness among people who use drugs (PWUD) included experience of intimate partner violence, younger age and multi-partnership. Enabling factors included receiving information from their doctors, and needs components were composed of increased perceived and behavioral HIV risk, depression, and neurological impairments. For PrEP awareness among PWUD, route of drug administration and sexual orientation were considered as predisposing factors, while discussing PrEP at a syringe exchange program was considered as an enabling component (Table 3).

Discussion

Our meta-analytic review included 755 WWUD from seven studies (604 from four women-only samples). The low awareness of PrEP among WWUD (21%) raises concern for this high-risk group, especially when considering this group may have frequent contact with harm reduction and health professionals via various encounters (e.g., settings providing needle exchanges and sexual health services [30], opioid detoxification programs [47], and methadone maintenance programs). However, once WWUD were informed of PrEP, their willingness to take PrEP increased considerably (60% for WWUD, and 57% for women who inject drugs). The discrepancy between lower awareness and higher willingness represents a missed opportunity for initiating PrEP among WWUD who are willing to take PrEP if they are well-informed. After including male drug users in the analyses, both PrEP awareness (20.6% vs. 17.2%) and willingness to use (60.2% vs. 52.1%) decreased slightly. Our findings suggest that WWUD's PrEP awareness were higher compared

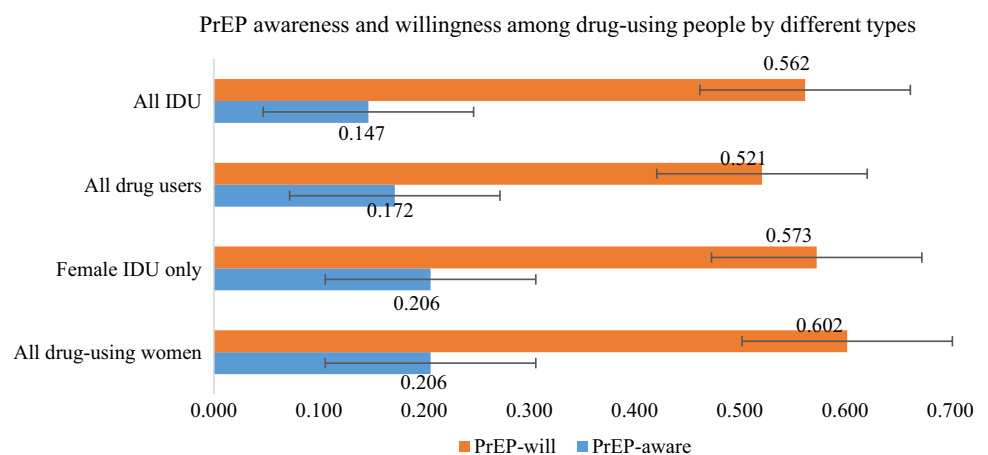**Table 2** Summary of meta-analyses among drug-using people

		Women drug-users		Men and women drug users	
		Women who use drugs[a]	Women injectors only	Men and women (mixed)who use drugs[a]	Men and women (mixed) injectors only
PrEP awareness	Pooled prevalence	20.6% (95% CI 8.7%, 32.4%)	20.6% (95% CI 8.7%, 32.4%)	17.2% (95% CI 12.0%, 22.4%)	14.7% (95% CI 9.5%, 20.0%)
	d.f. (n − 1)	3	3	7	5
	I^2 statistics	89.3% (75.4%, 95.4%)	89.3% (75.4%, 95.4%)	91.7% (86.2%, 95.1%)	89.7% (80.4%, 94.6%)
	Publication biases	Yes	Yes	Yes	Yes
Willingness of PrEP use	Pooled prevalence	60.2% (95% CI 52.2, 68.2%)	57.3% (95% CI 48.8, 65.9%)	52.1% (95% CI 42.8, 61.4%)	56.2% (95% CI 45.2, 67.2%)
	d.f (n − 1)	3	2	4	3
	I^2 statistics	65.1% (0.00%, 88.1%)	50.8% (0.00%, 85.8%)	90.5% (80.7%, 95.3%)	91.1% (80.4%, 96.0%)
	Publication biases[b]	Yes	Yes	Yes	Yes
Risk compensation	Pooled prevalence	n/a	n/a	26.1% (95% CI 6.9%, 45.2%)	18.4% (95% CI 9.9%, 26.8%)
	d.f. (n − 1)	n/a	n/a	3	2
	I^2 statistics	n/a	n/a	98.4% (97.5%, 99.0%)	98.9% (98.1%, 99.3%)
	Publication biases[b]	n/a	n/a	Yes	Yes

df degree of freedom

[a]Drugs including both injecting and non-injecting drugs

[b]Publication biases were assessed by funnel plots

Fig. 1 PrEP awareness and willingness among drug-using people by different types of drug use[a,b]. [a]pooled prevalence of PrEP willingness and PrEP awareness among different types of drug users (e.g., all injected drug users [IDU], all drug user including men and women, female IDU only, all drug using women) and its corresponding 95% confidence interval; [b]x-axis is the pooled prevalence (ranged from 0 to 0.70)

PrEP awareness and willingness among drug-using people by different types

- All IDU: PrEP-will 0.562, PrEP-aware 0.147
- All drug users: PrEP-will 0.521, PrEP-aware 0.172
- Female IDU only: PrEP-will 0.573, PrEP-aware 0.206
- All drug-using women: PrEP-will 0.602, PrEP-aware 0.206

■ PrEP-will ■ PrEP-aware

to male counterparts who use drugs, but lower compared to MSM (PrEP awareness ranged from 27 to 46% among MSM) [49–51]. On the other hand, WWUD's willingness was similar or higher than their male counterparts, but PrEP uptake among WWUD much lower than MSM [49–51]. This higher level of awareness and uptake among MSM may stem from various PrEP initiatives primarily focusing on this population; such initiatives have been lagging for individuals who use drugs. In settings where PWUD usually seek help (e.g., drug treatment services), it is highly plausible that health professionals could engage

their patients/clients about PrEP use through counselling and treatment referrals. For instance, in New York State the Department of Health has successfully initiated a PrEP service in established syringe exchange programs and sexual health clinics to assist high-risk individuals access PrEP care [52].

In addition to examining PrEP awareness and willingness to use PrEP, potential risk compensation was examined among men and women (mixed) who use drugs. Although < 20% of PWUD indicated they would "*no longer need condoms during sexual episodes or sterilized*

Table 3 Summary of factors associated with PrEP awareness and willingness among people who use drugs

Study	Predisposing components	Enabling components	Needs components
Peitzmeier 2017 (PrEP willingness)	Women IDUs: who experienced physical or sexual violence from clients were more likely to be interested in PrEP (86% vs. 53%, p=0.009); Women younger than 35 were somewhat more interested in PrEP than older women (77% vs. 53%, p=0.07)		All IDUs: PWID at higher risk of sharing cookers, cotton or water ([a]aOR 3.47, 95% CI 1.71, 7.06), who believe they no longer needs clean needles if using PrEP ([a]aOR 4.95, 95% CI 1.60, 15.32) were more willing to use PrEP. IDUs who had depressive symptoms reported to be very likely to use PrEP if it were available at no cost
Levin (2014), Kuo (2016) (PrEP willingness)	[b]All drug users: independent correlates of reporting being very likely to use PrEP included being younger (<50 years old; [a]aOR 3.05, 95% CI 1.44, 6.05) and having two or more sex partners in the past 12 months compared to having none ([a]aOR 5.03; 95% CI 1.82, 13.9).		
Metz (2017) (PrEP willingness)		[b]All drug users: effectiveness of the medication was the criterion that received the highest ratings of being the basis for their decision to take such a medication. About half of the sample would base their decision on the information they received from their doctor, whereas a slightly lower proportion of participants indicated experiences from other people who had taken the medication and information on the internet as decisive	
Shrestha (2016, 2017) (PrEP willingness)			[b]All drug users: drug users who had neurocognitive impairment ([a]aOR 3.184, 95% CI 1.459, 6.949), who reported moderate ([a]aOR 4.439, 95% CI 1.959, 7.060) or high ([a]aOR 8.044, 95% CI 3.012, 13.481) perceived risk of getting HIV are more likely to report to be willing to use PrEP
Stein (2014) (PrEP willingness)			All IDUs: higher perceived HIV risk and higher effectiveness scenario was associated with greater willingness to take medication
Walter 2017-NYC (PrEP awareness)	[b]All drug users: non-injection drug use, HIV status, and exposure to HIV prevention, males who inject drugs had significantly decreased odds of PrEP/PEP awareness [[a]aOR 0.45; confidence interval (CI) 0.25 to 0.81] compared with MSM. MSM aged 18–29 years had increased awareness of PrEP ([a]aOR 2.94; 95% CI 1.11 to 7.80). MSM aged 18–29 had increased PrEP awareness		
Walter 2017-LS (PrEP awareness)	Women drug users[c]: females who inject drugs ([a]aOR 0.18; 95% CI 0.05 to 0.62), female heterosexuals ([a]aOR 0.25; 95% CI 0.11 to 0.59) had significantly decreased odds of PrEP/PEP awareness. All drug users[b]: males who inject drugs ([a]aOR 0.14; 95% CI 0.05 to 0.39), and male heterosexuals ([a]aOR 0.32; 95% CI 0.14 to 0.73) had significantly decreased odds of PrEP/PEP awareness. Black MSM had increased awareness of PrEP ([a]aOR 4.08 CI 1.21 to 13.73)		
Walters 2017 (PrEP awareness)	Women IDUs: increased PrEP awareness was associated with reported transactional sex ([a]aOR 3.32, 95% CI 1.22–9.00).	Women IDUs: increased PrEP awareness was associated with having a conversation about HIV prevention at a syringe exchange program ([a]aOR 7.61, 95% CI 2.65–21.84).	

IDU injecting drug users

[a]aOR and 95% CI: adjusted odds ratios and corresponding 95% confidence intervals

[b]All drug users include both men and female drug users regardless of their drug administration routes

[c]Women drug users includes only women who use drugs regardless of their drug administration routes

needles during injections after PrEP use", these estimates were based on complete relinquishment of other forms of protection (e.g., elimination of condoms/clean needles after taking PrEP). If participants' perception of risk compensation was evaluated conservatively (e.g., reduction in the use of condom/clean needles), a majority of participants expressed potential tendency for risk compensation while taking PrEP [33, 45]. Though PrEP clinical trials have yet to observe any risk compensation behaviors [14, 53], increased prevalence of risky sexual behaviors (e.g., condomless sex, increased sexual partners) and sexually transmitted infections (STI) have been reported among PrEP users in several observational studies [54, 55]. However, none of the included studies contained data depicting gender-specific perceptions of potential risk compensation in these included studies. Future studies should closely monitor actual risk compensation behaviors among PWUD and are taking PrEP, and future PrEP implementation interventions targeting individuals who use drugs should include education on both the benefits and limitations of PrEP to avoid potential risk compensation behaviors.

Our meta-analysis has several strengths, including (a) it is the first study to synthesize PrEP awareness and willingness to use among WWUD as well as among all PWUD in the U.S. by subgroup analyses; (b) we employed the STATA *Metaprop* command with random effect models to accurately accommodate the within-study variances of binominal data; and (c) the PRISMA guideline was strictly followed throughout all procedures.

Several limitations of our review and findings should be noted, most of which derive from the limited number, geographic scope, and specificity of existing studies on PrEP among WWUD. These limitations constrained the representativeness and generalizability of our findings. First, of the seven included studies, all were conducted in urban areas in the Northeast U.S., no studies have been conducted among WWUD in the Deep South or rural areas, which have among the highest rates of HIV incidence and prevalence across the U.S. [56–58]. In addition, half of the included studies failed to provide gender-specific data [28, 29, 33, 45–47]. Even for studies with gender-specific data, WWUD were only a small proportion of all recruited participants [33, 45]. Thus, regional and gender under-representativeness may not reflect the full scope of sexual risk and HIV transmission dynamics among WWUD in the U.S.

Second, there is a lack of data regarding PrEP uptake, retention, and adherence among this at-risk group as a whole. Among all included studies, few participants reported PrEP use [31, 33, 45]. It is estimated that only 5.3% to 15.2% of high-risk individuals achieve sustained PrEP use, due to individual, social, and structural barriers interrupting the continuum of PrEP care [16, 59]. The scarcity of data

regarding the PrEP care continuum among WWUD requires future studies to address this gap.

Third, several included studies failed to report demographic-specific data regarding PrEP use among WWUD. Only one study examined racial differences in HIV risk factors, including PrEP awareness and willingness to use among individuals with opioid use disorders [46]. Lack of sufficient demographic-specific data regarding PrEP use may hinder the deployment of interventions tailored to WWUD with various cultural characteristics.

Fourth, half of the included studies employed secondary data analyses [28, 29, 31, 32], and those studies may not have been originally designed to assess PrEP awareness and willingness. In addition, the rest of the included studies employed convenience sampling strategies to recruit participants from settings providing health services (syringe exchanges and sexual health services [30], opioid detoxification programs [47], and methadone maintenance programs), which may have resulted in under-sampling of hidden and hard-to-reach subpopulations. Omission of these key subgroups may leave important gaps in our understanding regarding HIV epidemics and PrEP implementation in this population [60].

Lastly, the accuracy and reliability of the synthesized effect sizes of PrEP awareness and willingness to use may be affected by the significant heterogeneity, publication and self-reported biases, as well as inconsistent measurements and misclassification of key indicators across studies. For instance, some studies categorized "very likely and somewhat likely" as "willingness to use PrEP" [30, 47], whereas another study categorized "somewhat likely" as "no willingness to use PrEP" [28, 29]. Furthermore, some studies referred to PrEP simply as "a pill" or "anti-HIV medicines" [29, 30, 47, 61], whereas other studies specified PrEP as "Truvada" or "an antiretroviral medication" [31, 32, 46]. Furthermore, all measurements on "PrEP awareness*"* and "willingness to use" were based upon one single item, and were inconsistent across different studies: some studies asked the likelihood of taking PrEP in the future [33, 45], while another evaluated willingness based upon different hypothetical scenarios [47]. Inconsistent descriptions of PrEP, variations of the cut-off points, and the measurement's lack of comprehensiveness and consistency may lead to biased synthesized estimates.

Our systematic review revealed several critical deficiencies with regard to current evidence on the PrEP care continuum among U.S. WWUD, including the limited number, scope and specificity of extant studies, as well as limitations in study design. Despite these shortcomings, our meta-analysis provided empirical estimates for the initial two stages along the PrEP care continuum: "PrEP awareness" and "willingness to take PrEP." Since using PrEP can prevent women from sexual and blood-born

transmission of HIV, WWUD, in particular, would benefit from PrEP. Each phase of the PrEP care continuum cascade represents a potential barrier and critical intervention point to achieve sustained PrEP protection. In order to address limitations identified in the current review, we call for comprehensive assessment tools and standardized measures to evaluate each step of the PrEP care continuum among WWUD in future studies.

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