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ORIGINAL PAPER

Engagement Along the PrEP Care Continuum Among Men Who Have Sex with Men in China: A Systematic Review and Meta-analysis

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Abstract

Pre-exposure prophylaxis (PrEP), including daily oral, on-demand, and long-acting injectable (LAI), is a promising HIV prevention intervention for men who have sex with men (MSM). We conducted a systematic review on engagement with the PrEP continuum among MSM in China. A total of 756 studies were initially identified and 36 studies were included (N = 26,021). In the 20 studies (N = 13,886) examining PrEP awareness, 32.4% (95% CI: 25.1–40.7) of MSM were aware of PrEP. In the 25 studies (N = 18,587) examining willingness, 54.5% (95% CI: 41.9–66.5) MSM indicated they were willing to use PrEP. The pooled prevalence of PrEP uptake from 9 studies (N = 6,575) was 4.9% (95% CI: 1.4–15.8%), while pooled estimates of adequate adherence from five studies (N = 2,344) among MSM on PrEP was 40.7% (95% CI: 20.0-65.2%). Subgroup analyses suggested studies conducted after 2015 (versus before) tended to report higher awareness and uptake. Awareness was highest for daily oral PrEP, followed by on-demand, and LAI PrEP; willingness to use was highest for LAI PrEP. The operationalization of willingness and adherence constructs varied across studies and complicated the interpretation of pooled estimates. This review revealed gaps in the PrEP care continuum among MSM in China, with relatively low awareness and uptake (in contrast to willingness and adherence) as the major potential barriers to widespread implementation and the need for a unified approach to defining and measuring PrEP outcomes.

Keywords Pre-exposure Prophylaxis · PrEP · China · Men who have sex with men · MSM · Systematic Review

Liying Wang and Chenglin Hong contributed equally to this work and have the right to list their name first on their CV.

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Introduction

Gay, bisexual, and other men who have sex with men (MSM) are among the most vulnerable populations for HIV infection in China [1]. National surveillance reports indicate that MSM accounted for more than a quarter (26%) of new HIV diagnoses in 2017, which was twice as many as the proportion in 2007 [2]. Despite the efforts to prevent HIV transmission, however, HIV prevention interventions uptake remains low among MSM in China. A systematic review of HIV testing showed that more than 60% of Chinese MSM had not received an HIV test in the past year and nearly half of them had never in their lives been tested for HIV, despite the high rate of condomless anal sex among MSM in China [3, 4]. In addition, MSM face multilevel barriers to receiving HIV prevention services, including stigmatization of gay/bisexual identity, low perceived risk of HIV, medical mistrust and discrimination, concerns about privacy and confidentiality, and fear of HIV diagnosis [5–7].

HIV pre-exposure prophylaxis, or PrEP, a biomedical tool with a daily combination of two anti-HIV medications in one pill, is highly effective in preventing HIV acquisition among individuals at high risk of infection when taken as prescribed [8]. The three common modalities of PrEP include daily oral (PrEP taken every 24 h), on-demand (taken before and after sexual contact), and long-acting injectable (LAI, injection once every one to two months). The efficacy of daily oral and on-demand PrEP in reducing HIV incidence was demonstrated in medical trials across the world [9, 10]. Recent randomized control trials and modeling studies suggest LAI PrEP was non-inferior to oral PrEP regime in reducing HIV incidence [11, 12]. In 2015, the World Health Organization (WHO) recommended PrEP for HIV prevention for people at substantial risk including MSM [13]. It has estimated that by the third quarter of 2021, more than 1.5 million people would have initiated PrEP for HIV prevention globally [14]. Randomized clinical trials have demonstrated the efficacy of PrEP in preventing HIV among diverse populations including MSM when taken as prescribed [15]. Recent real-world studies in Australia and Scotland also demonstrated the population-level long-term efficacy of daily oral PrEP in maintaining and reducing the overall HIV incidence among adherent gay and bisexual men [16].

The PrEP care continuum framework has been previously developed and updated for program evaluation and implementation progress [17, 18]. The PrEP care continuum outcomes in this framework include awareness, willingness, uptake, and adherence. Despite the efficacy in preventing HIV infection and reducing HIV incidence among MSM, the progress of implementing PrEP has been relatively slow in China. In 2015, emtricitabine/tenofovir disoproxil fumarate/efavirenz (FTC/TDF/EFV) was introduced as a first-line ART regimen for HIV treatment [19]. In the same year WHO recommended PrEP for people at high risk for HIV [13]. However, it was not until August 2020 that Truvada (FTC/TDF) was approved for HIV prevention by the China National Medical Products Administration and became available to the public at a price of $310/month [20, 21]. The national guidelines for FTC/TDF were issued in 2021, detailing the indications, regimen, and precautions around PrEP use [22]. However, the lack of healthcare providers with expertise in sexual health of MSM and absence of insurance coverage limit the accessibility and affordability of PrEP [23].

Nevertheless, PrEP is a promising tool for HIV prevention in China. A modeling study suggested that in the next two decades, about 170,000 to 320,000 new HIV infections could be prevented if PrEP uptake among MSM in China reached 50% [24]. Studies on PrEP among Chinese MSM have started to emerge in the last few years. There is a lack of systematic summary of PrEP implementation in China across the four PrEP continuum outcomes, including PrEP awareness, willingness, uptake, and adherence. One systematic review on 54 studies found high acceptability of PrEP among Chinese MSM, which suggested high PrEP willingness but did not provide clarity on PrEP awareness, uptake and adherence [25].

The aims of this systematic review were to (1) assess the overall PrEP care continuum outcomes among MSM in China, including PrEP awareness, willingness, uptake, and adherence; and to (2) review the operationalization of the care continuum outcomes. The anticipated results of this review will fill in a critical gap in the literature and summarize existing evidence to inform the scale-up of PrEP and its clinical practice guidelines in China. Recommendations will be made based on the review of measurement to inform future assessment of care continuum outcomes.

Methods

Study Design and Registration

The review was designed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [26]. A study protocol summarizing the methods of this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021235651).

Search Strategy

We conducted a systematic search of published literature in both English (EN) and Chinese (CN) using the following databases: Pubmed, Embase, PsycINFO, CINAHL, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang Data. The last two databases were used to search for peer-literature articles in Chinese language. A combination of Medical Subject Heading (MeSH), phrases, and keywords targeting "pre-exposure prophylaxis or PrEP", "China", and "men who have sex with men" were developed to facilitate the literature research A complete search strategy was provided in Appendix 1. We executed the original search in March 2021 and updated the search in August 2022.

Eligibility Criteria

Studies were included if they (1) reported at least one of the PrEP outcomes in the continuum (i.e., awareness, willingness, uptake, or adherence); (2) were conducted in mainland China; (3) focused on men who have sex with men or reported outcomes for MSM if other populations were included; and (4) were published in English or Chinese. Given that China introduced Truvada (FTC/TDF) as HIV treatment medication in 2015 and WHO recommended PrEP for HIV prevention [13, 19], we included studies that were published since 2012 to examine the past 10 years of literature and capture the potential change in outcomes before and after 2015. We excluded studies that (1) focused only on testing the efficacy of PrEP among Chinese MSM, given that our focus on engagement with PrEP care continuum; and (2) only reported qualitative outcomes regarding engagement with PrEP continuum.

Study Screening and Selection

Database research results were imported into Covidence software. Duplicates were removed and the included studies were allocated among four reviewers, who independently screened titles and abstracts under blinded conditions. Studies that met the eligibility criteria progressed to full-text screening. Next, all four reviewers screened the full texts to determine the inclusion of the article in the review. Results of each review of titles, abstracts, and full texts were compared and discussed until consensus was reached.

Data Extraction and Quality Assessment

We created a standardized extraction form to manage the data and information from the included articles, including study characteristics and outcomes on the PrEP continuum. This study mainly focused on daily oral PrEP, given that it has the most data available. Pooled estimates were calculated for daily oral PrEP. Data on other types of PrEP was reported when available. Data extracted from each paper included title, publication year, language, study location, study design and sample recruitment methods, year data were collected, sample size, and participants' sociodemographic characteristics. Data on PrEP continuum outcomes extracted included, definition, measurement, and outcomes (percentages, means). The studies were allocated among four reviewers for data extraction and the results were discussed with the team to reach consensus.

As most of the included studies were cross-sectional, the quality of eligible articles was critically appraised independently by three reviewers using the Appraisal tool for Cross-Sectional Studies (AXIS) [27]. Three reviewers discussed the quality assessment results and reached consensus when discrepancies arose.

Statistical Analysis

A random-effects model was used to pool the proportions from primary outcomes, which is generally appropriate with the assumption that the proportions differ across all studies due to heterogeneity among studies [28, 29]. To examine the source of heterogeneity, subgroup analyses were performed to explore differences in PrEP continuum outcomes across studies grouped based on: (1) year of study conduction (year <2015 and year ≥ 2015); (2) study location (east, west, central). We chose 2015 as the threshold for subgroup analysis given the recommendation of PrEP use for HIV prevention by WHO and introduction of FTC/TDF for HIV treatment in China [13, 19]. China has four major economic regions, including northeast, eastern, central, and western regions [30]. We combine northeast and eastern regions into east due to geographical closeness and relatively leading economic development compared to the other two regions [31]. Regarding willingness, studies were also grouped based on the level of detail of PrEP description (simplified vs. detailed) to examine whether willingness to use PrEP differed across sub-groups of studies. No subgroup analysis was performed on adherence given the limited number of studies that reported this outcome. When meta-analysis was not applicable due to limited data points, we applied narrative synthesis to summarize the findings from individual studies that are relevant to the aims of the review. Specifically, we addressed the following questions using narrative synthesis: does the PrEP care continuum outcomes differ across different PrEP modalities; and what are the measurement questions and operational definitions of PrEP outcomes.

Results

Study Selection

Two rounds of the literature search were conducted (in March 2021 and August 2022), identifying 756 records in total, with 586 from English language databases (Embase, Web of Science, Medline, PubMed, PsychInfo, CINAHL) and 170 from Chinese language databases (WanFang Database, CNKI). A total of 237 duplicate titles were removed, leaving 519 for screening using the eligibility criteria. Among these, 340 articles were excluded after reviewing their title and abstract, leaving 179 articles for full-text review. After excluding articles based on eligibility criteria, 36 articles were included in this review. See Fig. 1 for the PRISMA flowchart of the study selection process.

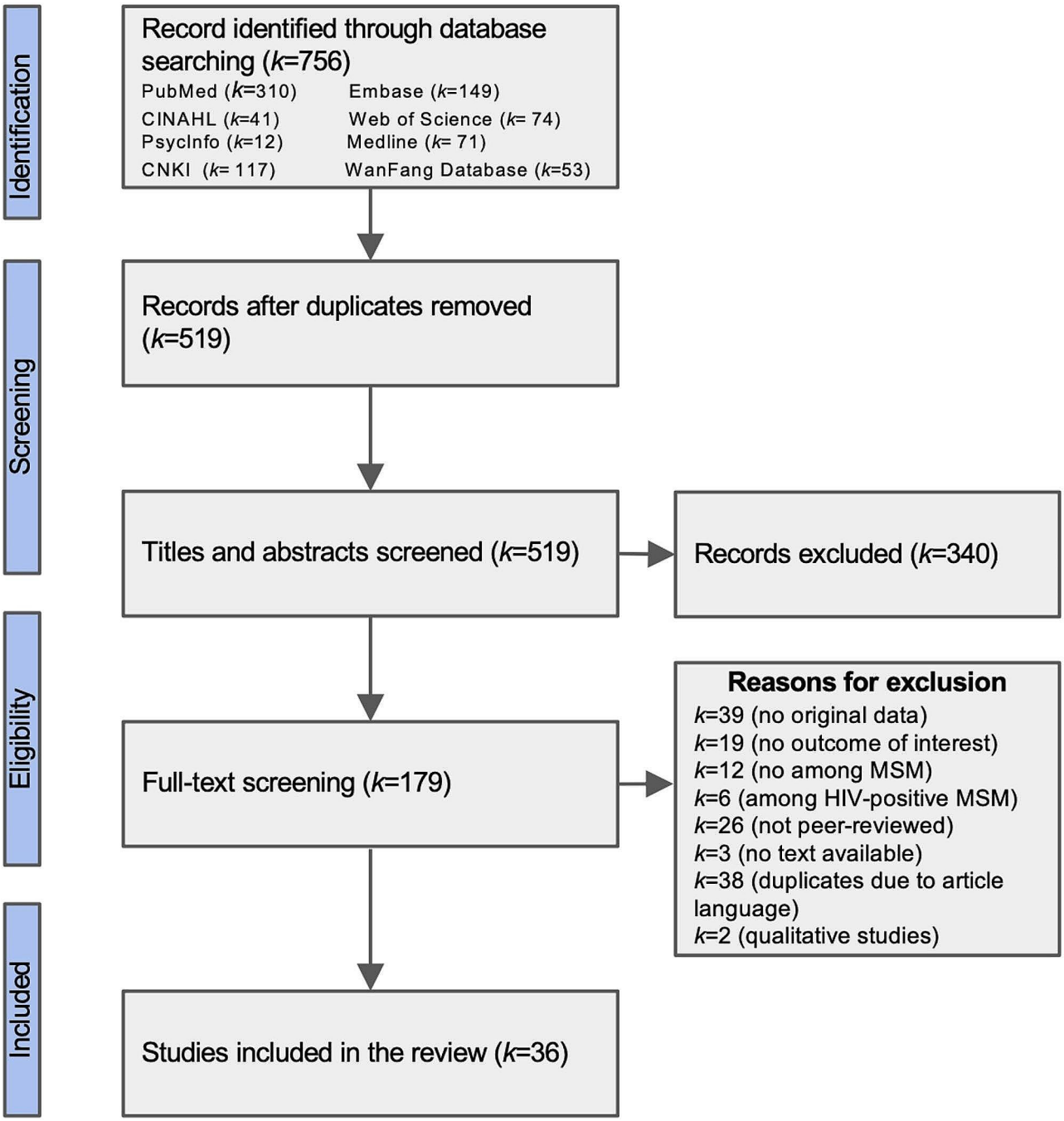

Fig. 1 PRISMA flowchart of search strategy and study selection

Study Characteristics

A total of 36 studies were included in this review (Table 1). Most ($k = 29$) were published in English, conducted in eastern ($k = 27$) and western regions of China ($k = 20$), and used cross-sectional survey methods ($k = 28$) and cohort studies ($k = 5$). Data from included studies were collected between 2009 and 2019, with over half ($k = 22$) collected after 2015, when Truvada (FTC/TDF) was approved for treatment in China (See Appendix 2 for detailed information about studies included in this meta-analysis).

Participant Demographics

Our systematic review included a total number of 26,021 MSM. One study only included MSM college students [32]. Age of participants in this analysis ranged from 15 to 85 years; 26 studies reported a mean or median age of MSM between 24 and 32. In most studies ($k = 28$, $N = 18{,}502$), more than half of the MSM had at least high school education and were not married. Among the studies ($k = 24$, 67%, $N = 19{,}067$) that reported sexual orientation of MSM, the majority of MSM participants identified as gay. Among the studies ($k = 8$) that reported the urban/rural residential status of MSM, seven of them ($k = 7$, $N = 4{,}083$) had more urban residents than rural residents. About half of the studies ($k = 17$, 47%, $N = 12{,}694$) indicated the inclusion of ethnic minorities (e.g. Zhuang ethnicity) in the sample. Four out of the 36 studies (11%, $N = 2{,}775$) had more than 70% of MSM participants reporting a monthly income less than 3,000 RMB (~471 USD).

Table 1 Study characteristics ($k = 36$)

Study Characteristics	*k* (%)
Language	
Chinese	7 (19.4%)
English	29 (80.6%)
Sample size	
Mean (SD)	723 (707)
Range	49–4142
Region	
East	19 (34.6%)
Central	5 (9.1%)
Northeast	7(12.7%)
West	22(40.0%)
Undetermined	2(3.6%)
Study design	
Case series	3 (8.3%)
Cross-sectional	28 (77.8%)
Prospective cohort	4 (11.1%)
Retrospective cohort	1 (2.8%)
Sampling method	
Convenience sampling	23 (63.9%)
Purposive sampling	2 (5.6%)
Snowball sampling	11(30.6%)
Year of study conducted	
2009–2014	12 (35.3%)
2015–2019	22 (64.7%)
N-Miss	2
PrEP definition	
Detailed	4 (23.5%)
Simplified	13 (76.5%)
NA[a]	19

[a] Studies that did not describe what information about PrEP was provided to study participants were marked as missing. Detailed PrEP definition refers to PrEP descriptions that included both positive (e.g. efficacy in HIV prevention) and negative (e.g., side effects) of using PrEP.

Bias Assessment

Three reviewers evaluated studies' quality using the Appraisal tool for Cross-Sectional Studies (AXIS) [27]. Different aspects of the studies assessed include whether the aims/objectives of the study are clear, whether the study is methodologically sound, whether the results are accurately and adequately reported, and whether the discussions and conclusions are justified by the results. There were no major concerns around quality for studies included in this review. Thus, all studies were included and the impact of their inclusion on the robustness of findings and conclusions was discussed.

Description of PrEP

All studies described PrEP prior to asking participants about PrEP-related questions. However, only half of the studies ($k = 18$, 50%, $N = 14{,}424$) presented the descriptions of PrEP provided to the participants in the paper. The information was either provided verbally by the researchers or using an information sheet distributed to the study participants. Among these studies, all provided basic information about PrEP, such as the purpose of taking it is to reduce the risk of HIV acquisition. Four studies provided additional information about PrEP such as types of PrEP (oral or injection), frequency (daily, on-demand, or every eight weeks), importance of adherence, side effects, and estimated costs [33, 34].

PrEP Care Continuum

Awareness

A total of 20 studies ($N = 13{,}886$) reported awareness of daily PrEP (Table 2). The pooled estimate of the awareness of daily oral PrEP was 32.4% (95% CI: 25.1–40.7). Heterogeneity test results suggested significant heterogeneity among the included articles ($I^2 = 98.3\%$, 95% CI: 98.0-98.6%).

Table 2 Pooled estimate and qualitative summary of PrEP outcomes

	Pooled Estimate of Daily oral PrEP		Individual studies on other PrEP modalities[a]	
	Pooled Estimates (%) (95%CI)	Heterogeneity (I^2, %)	On-demand PrEP (%)	LAI PrEP (%)
Awareness ($k=20$)	32.4 (25.1–40.7)	98.3	29.8 [26] 30.7 [27]	6.22 [26] 7.1 [27]
Willingness ($k=25$)	54.5 (41.9–66.5)	99.5	79.2 [27] 78.4 [23] 58.2 [28] 67.7 [26]	85.7 [29] 76.0 [30] 63.7 [23] 62.8 [27] 38.5 [24]
Uptake ($k=9$)	4.9 (1.4–15.8)	98.9	49.2 [31] 28.4 [32]	NA
Adherence ($k=5$)	40.7 (20.0-65.2)	98.6	77.8 [31] 65.0 [33]	NA

[a] Pooled estimates were not calculated due to limited number of studies on on-demand PrEP and LAI PrEP. Outcomes were directly extracted from individual studies

Table 3 Subgroup analyses for PrEP outcomes[a]

	k	Pooled estimates	95% CI	*I^2*	*Q*	*p*
Awareness						
Year of data collection					4.18	0.041
pre_2015	3	0.21	0.0658; 0.5026	91.3%		
post_2015	16	0.36	0.2728; 0.4548	98.5%		
Region					0.23	0.892
East/Northeast	9	0.34	0.2170; 0.4929	98.4%		
Central	4	0.35	0.1163; 0.6878	98.8%		
West	6	0.31	0.1994; 0.4477	96.8%		
Willingness						
Year of data collection					0.21	0.647
pre_2015	17	0.5419	0.3801; 0.6953	99.6%		
post_2015	6	0.4903	0.2931; 0.6906	99.1%		
Region					0.24	0.887
East/Northeast	4	0.5283	0.1227; 0.8997	99.3%		
Central	11	0.5195	0.3142; 0.7184	99.6%		
West	8	0.5846	0.3516; 0.7851	98.9%		
PrEP definition					0.45	0.666
Detailed	4	0.5889	0.3600; 0.7848	97.8%		
Simplified	9	0.5296	0.2731; 0.7713	99.6%		
Uptake						
Year of data collection					5.56	0.023
pre_2015	2	0.0149	0.0001; 0.6833	89.7%		
post_2015	6	0.0887	0.0164; 0.3628	98.4%		
Region					4.29	0.109
East/Northeast	3	0.2384	0.0032; 0.9678	99.6%		
Central	2	0.0418	0.0072; 0.2088	0.0%		
West	4	0.0193	0.0015; 0.2010	95.1%		

[a] No subgroup analysis was conducted for Adherence outcomes due to a small number of studies ($k=8$)

Awareness of daily oral PrEP ranged from 11.2% [35] to 43.1% [34]. Most studies ($k=16$) found awareness was lower than 50%. Only four studies reported a PrEP awareness above 50%, ranging from 56.4% (Shi, 2020) to 76.5% [36]. Two studies reported awareness of different types of PrEP, daily oral PrEP had the highest awareness (32.7%, 33.8%), followed by on-demand (29.8%, 30.7%) and LAI PrEP (6.2%, 7.1%) [33, 37] (Table 2).

Subgroup analysis suggested studies with data collected before 2015 (versus after 2015) found a lower awareness of daily oral PrEP ($Q=4.18$, $p=0.041$). The subgroup analysis on awareness outcome by region suggested no significant statistical difference across studies conducted in east, west, or central China ($Q=0.23$, $p=0.892$) (Table 3).

Awareness Definition and Measurement The operational definition of awareness was consistent across all 20 studies. Awareness was defined as whether the participants have heard of PrEP and measured by a single question with a binary response scale (yes/no; e.g. "Have you ever heard of PrEP?").

Willingness

Willingness to use daily oral PrEP was reported in 25 studies ($N = 18{,}587$) (Table 2). The pooled estimate of willingness to use daily oral PrEP was 54.5% (95% CI: 41.9–66.5). High heterogeneity presented among the included articles ($I^2 = 99.5\%$, 95% CI: 99.4–99.5%).The reported willingness for PrEP use ranges from 10.6% in Hefei [38] to 94.6% in Guangxi [39]. Sixteen out of 25 studies with willingness outcomes (64%) reported willingness higher than 50%.

Willingness to use multiple types of PrEP was assessed by seven studies (Table 2), including LAI PrEP, daily oral PrEP, and on-demand PrEP [33, 34, 36, 37, 40–42]. A qualitative synthesis suggested that willingness to use PrEP differed across different types of PrEP, with more people willing to use LAI and on-demand PrEP than daily oral PrEP. For example, Cao et al. found that willingness to use on-demand PrEP is highest (78.4%), compared to LAI (63.7%) and oral daily PrEP (61.1%) [33]. Lin et al. also found willingness to use on-demand PrEP (60.1%) was higher than daily oral PrEP (55%) [36]. A similar pattern was also reported in other studies. One exception is the study by Chen et al., which reported more participants reported to be willing to use daily oral PrEP (62.2%) than LAI-PrEP (38.5%) [34].

Subgroup analyses suggested no statistically significant differences between studies conducted before and after 2015 ($Q = 0.21$, $p = 0.647$), across east, west, or east central China ($Q = 0.24$, $p = 0.887$), or whether the studies offered detailed and more realistic description of PrEP that included side effects and costs ($Q = 0.45$, $p = 0.666$) (Table 3).

Willingness Definition and Measurement The operational definition of willingness differed across studies. Conceptual definition of willingness was not stated. For example, Lai and colleagues used "acceptance of PrEP" [32], while Ding and colleagues asked whether participants were willing to join the intervention cohort to receive PrEP [43]. In Huang's study, willingness was assessed by asking participants' interests in using PrEP [42]. Cao et al. and Lin et al. used questions related to willingness but used "acceptability" to summarize the questions intended to measure [33, 36]. Other studies used one single question such as "Will you choose to use PrEP in the future?" [34].

Among the 25 studies that reported willingness outcomes, 22 (88%) used a single item such as "Assuming that daily oral PrEP is effective and safe, how willing would you be to use it?", among which 16 (72.7%) used Likert response scale and the rest using binary response (yes/no). Three out of 25 studies (12%) used a validated scale with multiple items and a Likert response (e.g., "absolutely unwilling" to "absolutely willing") [36, 44, 45]. All three studies adapted the scale developed by Holt et al. [46]. Wang et al. used a 7-item scale to assess several aspects of willingness to take PrEP, including willingness to take PrEP to prevent getting HIV, take pills before and after sex, pay for PrEP and to take PrEP even if it wasn't 100% effective [44]. The 19-item scale used in Yu et al. was based on Holt et al. by taking into account PrEP availability in China and the findings from the qualitative section of the study [45].

The operationalization of PrEP willingness varied across studies using a Likert response scale (Appendix 2). 19 out of 25 studies used a Likert response scale, among which the majority (15, 78.9%) used 5-point Likert scale, 3 used 4-point Likert scale, and one used 7-point Likert scale. All studies with a Likert response scale dichotomized the outcome. However, studies differed widely in their approach of dichotomizing the Likert scale. 17 out of 19 studies clearly stated operationalization of willingness to use PrEP, among which 15 studies (88.2%) using score 4 and 5 ("definitely will" or "probably will") to indicate willingness. Two studies used the highest score of 5 ("absolutely will") to indicate willingness [38, 47]. One study included "maybe" into the "yes" category while the rest of the studies categorized "maybe" into "no" [48].

Uptake

Nine studies reported PrEP uptake outcomes ($N = 6{,}575$). PrEP uptake ranged from 0.4% [45] to 36.9% [49]. Most of the studies (6 out of 9) reported uptake lower than 5%. The pooled estimate of the proportions of MSM who reported uptake of oral PrEP was 4.9% (95% CI: 1.4–15.8%). Heterogeneity test results suggested significant heterogeneity among the included articles ($I^2 = 98.9\%$, 95%CI: 98.6–99.2%).

Subgroup analysis suggested that studies conducted after 2015 ($k = 6$) tended to report higher uptake percentage, compared to those conducted before 2015 ($k = 2$) ($Q = 5.56$, $p = 0.018$). Two studies reported uptake of daily oral and on-demand PrEP regimes and found slightly higher uptake of daily oral PrEP compared to on-demand PrEP: 34.0% vs.

32.9% in Wang et al., and 36.9% vs. 28.4% in Meyers et al. [49, 50].

Uptake Definition and Measurement Similar to other PrEP outcomes, only operational definition of uptake was described in the studies. In 6 studies, PrEP uptake was measured by asking participants to report whether they have used PrEP to prevent HIV infection prior to taking the survey. In the other three studies, PrEP uptake was reported as the actual number who started using PrEP during a cohort or clinical trial [43, 49, 50].

Adherence

Eight studies reported PrEP adherence outcomes. Five studies calculated an adherence score to categorize participants into high/good adherence versus low adherence groups and reported frequency data. Three studies without raw frequency data were not included in the pooled estimate of adherence outcomes, did not have high/poor adherence categories, or measured perceived adherence rather than actual adherence [33, 50, 51]. No subgroup analysis was conducted due to the limited number of studies reporting adherence outcomes.

The rate of high or good PrEP adherence across the five studies ranges from 14.5% [52] to 62.1% [53]. The pooled estimate of the good PrEP adherence in the five studies ($N = 2{,}344$) was 40.7% (95% CI: 20.0-65.2%). There was significant heterogeneity across studies ($I^2 = 98.6\%$ 95%CI: 97.9–99.0%]. Wang et al. and Liu et al. reported adherence results for both daily oral PrEP and event driven PrEP [50, 54]. Both reported relatively higher percentages of good/high adherence among participants taking on-demand PrEP (77.8%, 65.0%) compared to those on daily PrEP (72.1%, 54.0%).

Adherence Definition and Measurement Studies reported the operational definition of adherence without a conceptual definition. For example, Wang et al. [50] defined adherence as taking PrEP as prescribed for at least 90% of days of self-reported sexually active (See Appendix 2 for details). Five out of eight studies used a similar formula to calculate adherence score within a certain amount of follow up time [50, 52, 53, 55]. Specifically, adherence score was calculated with the total number of pills taken divided by the total number of pills that should have been taken (or pills that had been prescribed) during the follow up period. All five studies used a threshold to category participants into good/high adherence and poor/low adherence groups. However, the adherence rate used as threshold differed across studies, including ≥ 60% in Liu et al. [54], ≥ 80% in Qu et al. [55] and Wu et al. [52], and ≥ 90% in Gao et al. [53] and Wang et al. [50]. All five studies measured missing doses using self-reported data. Additionally, Studies varied regarding the range of follow-up lengths, from 7 months [53] to 24 months [56].

Although Gao et al. [57] reported frequency data on good/poor adherence and thus was included in the analysis, the definition of adherence was unclear. Gao et al. defined poor adherence as having missed doses among daily PrEP users without clearly stating the number of doses required to be missed to count as poor adherence.

Discussion

This meta-analysis reviewed the literature in the past decade on all four steps of the PrEP care continuum among MSM in China, including PrEP awareness, willingness, uptake, and adherence. Overall, the contrast between higher willingness and lower awareness as well as higher adherence and lower uptake suggests a gap in linkage to care within the PrEP care continuum. The majority of studies focus on the care continuum around daily oral PrEP. The pooled estimates in this study showed that about one third of MSM in the reviewed studies were aware of oral PrEP and about half expressed willingness to use daily oral PrEP. Uptake was less prevalent with a pooled estimate of 4.9%. The percentage of high adherence rate was 40.7% based on the pooled estimate. All four outcomes had high heterogeneity, which could be attributed to study characteristics (e.g. year of study conducted) and measurement variation across studies. PrEP outcomes also differ across different modalities of PrEP regimes, with daily oral PrEP receiving highest awareness, long-acting injectable (LAI) PrEP having highest willingness, and on-demand PrEP having higher uptake and adherence.

Awareness of PrEP was low among the participants in the studies included in this review. We could not locate any previous review that focused on awareness of PrEP among MSM in China. Nevertheless, the proportion of PrEP awareness found in our review, 32.4% (95% CI: 25.1–40.7%), is similar to what reported by Yi et al. [58], 29.7% (95% CI: 16.9–44.3), which reviewed 13 studies from low- and middle-income countries, including China, Brazil, Thailand, Myanmar, India and Peru, with few counties reporting little or no awareness of PrEP among MSM participants. The wide range of awareness results in our study is 17.3–76.5%, which is also similar to what found by Yi (2017), 0% ~ 72.8%. Similar to Yi et al., awareness results from this review are highly heterogeneous. We found that the studies conducted after 2015 tended to report higher awareness

of PrEP. This might be due to the official introduction of TDF/FTC for HIV treatment in China in 2015 [20, 59]and the recommendation from WHO to use PrEP for HIV prevention [13]. Similarly, Sun et al. [60] found that studies conducted after 2014 tended to report higher percentages of PrEP awareness, which might be due to the recommendation issued by WHO in 2015. With only two studies on awareness of multiple modalities of PrEP, we were not able to conduct subgroup analyses to examine whether the awareness differs across PrEP modalities. Nevertheless, both studies found highest awareness of daily oral PrEP, followed by on-demand and LAI PrEP. This is consistent with the finding in Sun et al. [60], which reported a significant difference in awareness, with daily oral being the highest and LAI PrEP lowest.

The pooled estimate for willingness to use daily oral PrEP of 54.5% in this study is slightly lower than what was reported in a review of PrEP willingness among MSM in low and middle-income countries, (64.4%, 95% CI: 53.3–74.8) [58] and similar to what was reported by Sun et al. [60], who reviewed 156 studies across 145 countries between 2009 and August 2021 (54.4%, 95% CI: 42.4–66.4). Both Yi et al. and Sun et al. suggested that the proportion of willingness to use PrEP is higher among participants from lower income countries, compared to those from higher income countries. Sun et al. [50] hypothesized that this difference could be due to more concerns around privacy and PrEP stigma in high-income countries. However, literature on HIV-related and PrEP-related stigma suggests that it is also prevalent in low income countries, and is often a major barrier to PrEP acceptability and usage [61, 62]. A plausible explanation for this might be due to the increased options and resources available for HIV prevention in high-income countries, where individuals seeking HIV prevention are not limited to daily oral PrEP. This explanation is partially supported by this meta-analysis, where studies that examined willingness of using different types of PrEP consistently found higher willingness to use on-demand PrEP or LAI PrEP, compared to daily oral PrEP. Similar to Sun et al., we did not find the year of study data collection to be associated with PrEP willingness.

We found high heterogeneity of PrEP willingness among studies, which was also reported in the meta-analysis on PrEP willing across 145 countries [60] and within China [25, 63]. The wide range of willingness to use oral PrEP found in our review (10.6–91.8%) could be due to the different conceptual definition, operationalization, and measurement of willingness across the studies included in this review. In the studies we reviewed, studies equated willingness conceptually to constructs that are different from willingness, including acceptance of PrEP [32], interest in using PrEP [42], or acceptability of PrEP [33]. Only three out of 25 studies used a scale with multiple items that captures multiple dimensions of willingness (e.g., willingness to pay; willingness to use if not as effective). Using a single question to measure willingness is not sufficient to capture actual willingness, especially when the question is framed as hypothetical and in an ideal scenario (e.g., "Assuming that daily oral PrEP is effective and safe, how willing would you be to use it?"). Indeed, willingness to use PrEP decreased as the participants took into consideration mild and short term side effects such as headaches and diarrhea [24], taking into account the cost and after removing 100% efficacy [64]. The operationalization of PrEP willingness based on the dichotomization of the 5-point Likert response: some studies included "uncertain" into the "willing" category while others did not; some used the highest category to indicate willingness while others used second to highest. This further increases the difficulty of interpretation of the pooled estimation of willingness and contributes to the wide variation across studies in willingness to use PrEP.

Although we were not able to conduct subgroup analysis due to the limited number of studies, we observed that willingness varies depending on the types of PrEP, with a preference on LAI PrEP and on demand PrPE over daily oral PrEP. This is reversed compared to our findings of awareness of different types of PrEP, where LAI PrEP ranked lowest on awareness. In other words, MSM tend to prefer the LAI PrEP regime but only a very low percentage of people are aware of this PrEP modality. As daily oral PrEP was only approved in China in 2020 and studies on LAI PrEP are emerging, concerted efforts are needed to convey this modality of PrEP to increase public awareness of this potentially high acceptable PrEP regime. Recent trials on the LAI PrEP regime suggested that the LAI PrEP regime was found to be highly acceptable to participants due to its significant reduction in pill burden, keeping in mind the sampling bias where individuals not willing to receive injections would not enroll in the trial [65]. A review found a relatively higher willingness to use LAI PrEP and daily oral, compared to on-demand PrEP, although this difference was not significant [60]. This could be due to the small number of available studies on LAI PrEP, and further research is needed.

Only 4 out of 36 studies in this meta-analysis reported the detailed definition or introduction of PrEP to participants before assessing their willingness. The rest either omitted the information in their manuscript or provided simple and idealized definition (e.g., "Oral HIV pre-exposure prophylaxis (PrEP) is a promising biomedical HIV prevention approach in which HIV negative individuals take an oral antiretroviral medication daily to prevent HIV.") It is important to present a complete and realistic picture of PrEP (e.g., frequency of dosing, pain level for long acting injectable) so that participants could provide informed responses, which result in

accurate assessment of willingness. Further meta-analysis could examine whether detailed and realistic description of PrEP that includes information such as cost and side effects was associated with lower willingness to use it.

The number of studies that reported uptake ($k=9$) and adherence ($k=8$) outcomes is half of those that reported awareness ($k=20$) and willingness ($k=25$) outcomes. Only two studies reported on multiple types of PrEP. The limited data suggests relatively low uptake (below 5%). The three studies with high uptake might be due to the study being conducted on regions and key populations with high HIV prevalence or study design being cohort study and non-randomized control trial (Lai, 2020; Mayers, 2021; Wang, 2022). Adherence data, when available, suggested rates of good adherence to daily oral regime was about 40%. However, the inconsistent operationalizations and reporting of adherence outcomes across studies increased the difficulty to synthesize and interpret the results across studies. The limited data on and low rates of uptake and good adherence is reasonable given that the first PrEP pilot program in China was in 2018 [20]. The relatively low awareness and uptake compared to higher willingness and adherence might reflect a gap in the care continuum that requires more studies and implementation strategies to improve the linkage to care to improve awareness and uptake [66].

Many factors contribute to the limited engagement across the PrEP continuum among MSM in China. At individual level, lower perceived vulnerability and lack of HIV prevention literacy were linked to lower awareness and willingness to use PrEP, while higher education and perceived high risk of contracting HIV were linked to high willingness to use PrEP [37, 45]. Related, perceived limited effectiveness of PrEP on preventing HIV transmission and concerns around side effects were associated with lower willingness to use PrEP [34, 51]. At community and institutional level, MSM face discrimination from health care providers, which presents as a barrier to individuals' willingness to use PrEP [36]. At the structure level, high medication cost and limited health insurance coverage for PrEP further limited the willingness to use PrEP among MSM in China [36, 67]. For example, one study reported that only 5.5% of 1,915 participants indicated willingness to pay $150/month for PrEP, which is half of the price estimated for daily oral PrEP ($310/month) [21, 68].

There are several recommendations on further research based on the gaps in the literature identified through this meta-analysis. First, most studies focus on awareness and willingness to use PrEP, with little data on uptake and adherence. As China has only started implementing PrEP programs in the past few years, collecting baseline data on PrEP uptake and adherence is important to evaluate the success of future improvements on service delivery and implementation of PrEP programs. Second, there is a lack of literature that assesses awareness and willingness of different types of PrEP regimes. This information, coupled with assessment of acceptability and feasibility of PrEP programs, can inform decision making on development of PrEP delivery programs to multiple PrEP options to suit individuals' unique needs. Third, the lack of unified definition, measurements, and reporting of willingness and adherence created challenges for researchers to synthesize the highly heterogeneous results and extract meaningful conclusions. The field is in urgent need of an agreement on definition and measurements of PrEP continuum outcomes.

Limitation

Despite the rigorous methods we used following the PRISMA guidelines, our systematic review has a few limitations. First, due to the small size, subgroup analyses were not conducted such as comparing PrEP-related outcomes between young MSM vs. older MSM. Second, although we searched studies in both English and Chinese databases, it is possible that some studies were overlooked, especially for those written in Chinese. This may particularly be a selection bias for gray literature that is less likely to be published in peer-reviewed journals. Lastly, due to the heterogeneity of methods in calculating PrEP adherence score, we opted to use rates of good adherence as defined by the studies to calculate pooled estimates. However, this might not be a straightforward way to represent adherence.

Conclusions

We identified a gap between public knowledge of PrEP and PrEP uptake among MSM in China, indicated by the relatively higher awareness and willingness of using PrEP to prevent HIV acquisition compared to lower uptake and adherence. More research is needed to evaluate and implement PrEP programs to bridge the gap in care continuum, given limited literature to date and only recent approval for PrEP use in China. Awareness of PrEP increased in recent years, under the influence of PrEP related policies in China. The PrEP continuum outcomes differ depending on PrEP modalities. The relatively low awareness and high willingness of LAI PrEP indicates a need to expand PrEP-related health education and improve public awareness of PrEP modalities. The field is in urgent need for consistent definition, coherent operationalization, validated measurement, and agreed-upon reporting to allow for more accurate synthesis and interpretation of meta-analysis and reviews and to provide insight to program development and evaluation.

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Data Availability Data and material will be available upon request. Please contact liyingw@uw.edu with any requests.

Code Availability Code will be available upon request. Please contact liyingw@uw.edu to request code.

Declarations

Conflicts of Interest/Competing Interests Authors declare no competing interests.

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