Abstract

The appropriate use of pre-exposure prophylaxis (PrEP) by men who have sex with men (MSM) can be highly effective at reducing HIV transmission. Our review examined prevalence estimates, sexual behaviors, and medication adherence among MSM PrEP users in high-income countries. Papers published between January 2008 and December 2018 were identified through Medline, Web of Science, CINAHL, and Central. The search identified 643 publications, of which 52 were included in the final synthesis. We found that PrEP initiation was not consistently associated with significant changes in sexual behavior, but some users may have risk compensated. A minority of MSM used PrEP and they had high levels of adherence. PrEP-related stigma, side effects, and psychosocial factors lead to non-adherence. A daily routine, pill boxes, alarms/texts, and education can promote adherence. Further research is required to examine PrEP impact on sexual behavior and factors that influence adherence in high-risk MSM sub-populations.

Keywords. medication adherence, men who have sex with men, pre-exposure prophylaxis, review

Pre-exposure prophylaxis use and medication adherence among men who have sex with men: A systematic review of the literature

In 2016, there were more than 26,000 new HIV diagnoses in Western Europe; in the United States there were more than 38,000 new HIV diagnoses (Centers for Disease Control and Prevention [CDC], 2017; European Centre for Disease Prevention and Control, 2017). Men who have sex with men (MSM) are a minority in the populations of the United States and Western Europe but are at higher risk of HIV transmission compared to the general population. In Western Europe, MSM accounted for 45% of new HIV diagnoses and, in the United States, MSM accounted for 67% of new HIV diagnoses (CDC, 2017; European Centre for Disease Prevention and Control, 2017). The development of effective pre-exposure prophylaxis (PrEP) is an important HIV prevention strategy for MSM.

In 2012, the U.S. Food and Drug Administration was the first to approve PrEP for high-risk groups (CDC, 2014). In 2014, the United States published guidelines recommending that PrEP be provided to uninfected MSM who were not in a mutually monogamous relationship and had either had condomless anal intercourse (CAI) or been diagnosed with a sexually transmitted infection (STI) in the previous 6 months (CDC, 2014). In 2015, France implemented PrEP through the national health care system, and in 2016, the European Medicines Agency provided authorization for PrEP use in European Union countries (Eurosurveillance, 2018). Since that time, a few European countries have implemented PrEP through their national health care systems (Eurosurvelliance, 2018).

Since the introduction of PrEP, concern has been raised about risk compensation or changes in levels of high-risk sexual behavior because of PrEP

(Blumenthal & Haubrick, 2014). The key public health concern following PrEP initiation has been related to a potential increase in STIs (Blumenthal & Haubrick, 2014). Proxy measures such as changes in sexual behavior are often used in research, but the public health focus must be on any increase in STIs.

PrEP effectiveness and efficiency in reducing HIV in MSM will depend on uptake and adherence for those at highest risk. To date, there has been no comprehensive systematic review to synthesize what is known about prevalence of PrEP use, sexual behaviors, and biopsychosocial factors associated with PrEP adherence in MSM. We examined biopsychosocial factors associated with PrEP that have influenced medication adherence by MSM in high-income countries. Our objectives were:

1. To define prevalence estimates for PrEP use in MSM;
2. To identify factors associated with PrEP use, including socio-demographics and reasons/motivators for PrEP initiation;
3. To describe high-risk sexual behaviors and STI rates in PrEP users;
4. To identify levels of adherence in episodic and continuous dosing regimens; and
5. To describe the biopsychosocial factors that influence PrEP medication adherence and non-adherence.

Methods

Search Strategy

Our systematic review was conducted and reported in accordance with the Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA; Liberati et al., 2009). Four databases (Medline, CINAHL, Web of Science, CENTRAL) were used

because they included medical, nursing, allied health professional, sociological, and clinical trial journals. Search terms were generated based on the population (men who have sex with men, homosexual men, gay men, gay males), intervention (pre-exposure prophylaxis, PrEP), and outcomes of interest (adherence, non-adherence, concordance, compliance). All possible combinations of MeSH terms, MeSH headings, keywords, and phrases were used. The search was conducted in January 2018.

Eligibility Criteria

We included research that (a) examined actual use (as opposed to intended use) of PrEP; (b) had a sample of uninfected MSM; (c) were from high-income countries as defined by The World Bank (2019); (d) were primary research, fully published in peer reviewed journals; (e) had cross sectional, cohort, case control, qualitative, or randomized controlled trial (RCT) designs; and (f) were published in English from January 2008 through December 2017.

Ethical Considerations

As per the institutional ethics guidelines, ethics approval was not required as this was a review of peer reviewed published literature.

Study Selection and Data Extraction

One reviewer conducted the search using a predefined protocol developed with two senior researchers. Data retrieved through the search were extracted into Endnote x8 (Thomson Reuters, New York, USA). At the abstract stage, an independent reviewer examined a random sample of abstracts (10% of excluded and 20% of included articles) to ensure robustness of inclusion and exclusion criteria. All

differences were discussed and resolved. Data from the articles included in the final syntheses were extracted by one reviewer into a structured template.

Data Analysis

We synthesized evidence from studies that used a range of research methods and had wide variances in exposures/outcomes. A four-stage framework and techniques were used to increase transparency and trustworthiness of the narrative synthesis (Popay et al., 2006), and to compare and synthesize evidence in the review. The Antecedent, Behavior, and Consequence (ABC) framework was used to (a) understand predictors that may have occurred before an event (antecedents), (b) describe the process involved in an event (behavior), and (c) determine what factors might be outcomes of the event (consequences; Meaden, Ayvazo, & Ostrosky, 2014). Table 1 contains a provisional ABC analysis of PrEP use drawn from the literature and research team discussions.

Quality Assessment

Three validated tools were chosen to appraise the quality of studies included in the review's final synthesis: (a) the National Heart, Lung and Blood Institute (NHLBI, 2019) tool assessed cohort/cross sectional studies, (b) the Effective Public Health Practice Project (2019) tool assessed RCTs/controlled clinical trials, and (c) the Critical Appraisal Skills Programme (2019) qualitative checklist assessed qualitative studies. All three also assessed clarity and rigor of outcomes/measures, sample recruitment, data collection, analysis, ethical considerations, and findings.

Results

Study Selection

The number of studies identified, reviewed, selected, and reasons for exclusion are summarized in Figure 1. The initial number of articles captured from the search was 1,071; 52 articles were included in the final review.

Study Characteristics

Table 2 provides a summary of the aim, population, country, sample size, year of data collection, study design, appropriate overall quality rating, and ABC findings of the 52 articles included in the review. Figure 2 provides a summary of our main findings, which is structured using the ABC framework. The majority of the studies were from the United States (44); other studies were from Canada/France (3), Switzerland (1), France (1), United Kingdom (1), Canada (1), and Australia (1). The majority were cross sectional (25) or cohort (12) in design; the remaining studies were qualitative (9) or RCTs (6).

Study Quality

The majority of the cross-sectional studies had a fair quality rating, which, on the NHLBI tool means that a study could be susceptible to bias, but the findings were relevant; strengths and weaknesses were specific to each paper (NHLBI, 2019). Most reports did not provide sample size justification, measured exposures only once, and were unclear if researchers were blinded to the status of the sample. The primary strengths in most studies were clear objectives, defined exposures and outcomes, and appropriate methods for data analysis.

Most of the cohort studies were rated as good in quality, which is the best

NHLBI quality rating and means studies have a minimal level of bias and the findings are valid (NHLBI, 2019). The key strengths of the cohort studies were analysis of different exposure levels and exposures were measured more than once. Limitations in most of the cohort studies were the lack of sample size justification and not being clear if researchers were blinded to the sample status.

The Critical Appraisal Skills Programme qualitative tool does not provide an overall quality level of rating. However, the majority of qualitative studies provided a clear recruitment strategy, justified data collection methods, had ethics approval, described a rigorous analysis method, and provided findings in a clearly structured format. Most did not examine wider ethical issues raised in or from the study.

Most of the RCTs were rated as moderate in quality, which means studies have a robust and valid design, but a component in the study design had limitations (Effective Public Health Practice Project, 2019). The primary strengths of these studies were clear methods of randomization, no differences in study groups, sample blinded to the study outcome, and sample retention greater than 80%. Most were limited by not describing the reliability and validity of study assessment tools.

Prevalence of PrEP Use

Twenty studies from the United States (17), France (1), Australia (1), and Switzerland (1) examined prevalence estimates of PrEP use by MSM. Sample sizes ranged from 157 to 6,483 and all were cross sectional in design. The sample was heterogenous, as studies examined a variety of MSM populations using different recruitment techniques, with varied attempts to ensure representativeness. For example, some studies specifically recruited young MSM (YMSM) or minority racial/ethnic MSM, and the location of recruitment in some studies was primarily at

gay-centric venues. PrEP prevalence estimates ranged from 0% in a U.S. study conducted in 2004, to 12% in a U.S. study conducted in 2014 (Chen, Snowden, McFarland, & Raymond, 2016; Goedel, Halkitis, Greene, Hickson, & Duncan, 2016).

Five U.S. studies collected data prior to 2012 and reported a PrEP prevalence estimate range of 0% to 1.5% (Chen et al., 2016; Hood et al., 2016; Liu et al., 2008; Patrick et al., 2017; Rucinski et al., 2013). Fourteen U.S. studies conducted during or after 2012 identified a prevalence range of 1.5% to 12%, although the majority of the higher estimates (9%-12%) came from five studies that collected data in 2015 (Bauermeister, Meanley, Pingel, Soler, & Harper, 2014; Eaton et al., 2017; Goedel, Halkitis, Greene, & Duncan, 2016; Goedel, Halkitis, Greene, Hickson et al., 2016; Gupta, Lounsbury, & Patel, 2017; Holloway et al., 2017; Hoots, Finlayson, Nerlander, & Paz-Bailey, 2016; Klevens et al., 2017; Kuhns, Hotton, Schneider, Garofalo, & Fujimoto, 2017; Mayer et al., 2016; Oldenburg et al., 2016; Snowden, Chen, McFarland, & Raymond, 2017; Strauss et al., 2017). The highest estimate of approximately 12% from two studies included one small sample recruited via an MSM geo-social networking application and the other was a sample of YMSM (< 30 years of age; Goedel, Halkitis, Greene, Hickson et al., 2016; Kuhns et al., 2017). With the exception of these studies, the 2015 estimated range of PrEP prevalence was approximately 9% to 10%. It appeared that MSM samples reported increasing use of PrEP following U.S. approval of PrEP in 2012 and guidelines for high-risk groups in 2014.

Studies from France, Australia, and Switzerland reported a prevalence estimate range of 2% to 5% (Castro et al., 2017; Hampel et al., 2017; Zablotska et al., 2013). Data collection dates in these studies ranged from 2011 to 2017, but the two more recent studies (2014-2017) from Western Europe reported a range of 4%

to 5% (Castro et al., 2017; Hampel et al., 2017). The Australian study in 2011 found that 2.5% of the MSM sample were using PrEP (Zablotska et al., 2013). However, this study may not be generalizable to wider MSM populations as it recruited men from gay venues/events and sexual health clinics. Due to limited evidence, it was not possible to determine the precise prevalence of PrEP use amongst MSM outside of the United States.

Socio-Demographics of MSM PrEP Users

Twenty-seven studies reported or examined key socio-demographics of MSM who were using or had previously used PrEP. The majority were U.S. studies, which consisted of different designs: cross section to RCT. Sixteen studies did not recruit samples of a specific age and reported a median or mean age of PrEP users from 27 to 42 years (Arnold et al., 2017; Chan, Glynn, et al., 2016; Chan, Mena, et al., 2016; Collins, McMahan, & Stekler, 2017; Gilmore et al., 2013; Gupta et al., 2017; Hojilla et al., 2016; Marcus et al., 2016; Mayer et al., 2017; McCormack et al., 2016; Molina et al., 2015; Montgomery et al., 2016; Oldenburg et al., 2017; Parker et al., 2015; Storholm, Volk, Marcus, Silverberg, & Satre, 2017; Volk et al., 2015).

Three studies reported that no age was significantly associated with PrEP use (Hoots et al., 2016; Strauss et al., 2017; Zablotska et al., 2013), but, two U.S. studies identified PrEP use as more common in older men (Doblecki-Lewis et al., 2017; Snowden et al., 2017). These two studies may be limited in generalizability to the PrEP-using population as they had relatively small samples. From the evidence, PrEP use peaked in the late 20s to early 40s but was used across all ages.

Nineteen studies provided a breakdown of race/ethnicity; 13 of these studies reported that most participants were White (Chan, Glynn, et al., 2016; Chan, Mena,

et al., 2016; Collins et al., 2017; Doblecki-Lewis et al., 2017; Gilmore et al., 2013; Hojilla et al., 2016; Kuhns et al., 2017; Marcus et al., 2016; Mayer et al., 2017; McCormack et al., 2016; Montgomery et al., 2016; Oldenburg et al., 2017; Parker et al., 2015). Two U.S. studies reported that Whites were more likely to use PrEP compared to other races/ethnic groups (Hoots et al., 2016; Snowden et al., 2017). A study from the United States identified Black race as negatively associated with PrEP use (Kuhns et al., 2017), although this study only focused on YMSM. In contrast, an Australian study reported that minority racial/ethnic groups were more likely to use PrEP than Whites (Zablotska et al., 2013) and another U.S. study of YMSM reported that race/ethnicity was not associated with PrEP use (Strauss et al., 2017). In comparison, Strauss et al. (2017) had a sample size of 759 and Zablotska et al. (2013) had a sample size of 3,677. Overall, population representative evidence base was limited, and it was not possible to determine if there was an association between race/ethnicity and PrEP use.

Reasons and Motivators for PrEP Initiation

Twelve studies examined MSM reasons for starting PrEP. One study was an RCT and the primary reason for being involved in the study was to provide something meaningful back to the community (Gilmore et al., 2013). As this study was a trial, it may not help to understand key motivators for PrEP use. Three studies found that people started PrEP because they had or would be having multiple sex partners (Arnold et al., 2017; Holloway et al., 2017; Strauss et al., 2017) and four studies reported that a motivator for some MSM was that they had previously had or would have sex with partners whose HIV status was unknown or positive (Chan, Glynn, et al., 2016; Holloway et al., 2017; Kuhns et al., 2017; Strauss et al., 2017).

Two studies found that a history of having CAI or inconsistent condom use was associated with PrEP uptake (Collins et al., 2017; Kuhns et al., 2017); another study found that some men used PrEP because it allowed them to not use condoms (Taylor et al., 2014).

Five studies found that a central motivator for starting PrEP was to remove the anxiety of contracting HIV (Hojilla et al., 2016; Holloway et al., 2017; Hosek et al., 2013; Malone et al., 2017; Mimiaga, Closson, Kothary, & Mitty, 2014), but one U.S. study found no factors significantly associated with initiating PrEP (Chan, Mena, et al., 2016). The evidence suggests that planned high-risk sexual behaviors and removing anxiety related to contracting HIV motivated MSM to start PrEP.

Sexual Behavior

Twenty-seven articles, the majority of which were from the United States, examined aspects of high-risk sexual behavior. Eight studies reported CAI rates for PrEP users (27% - 87%; Castro et al., 2017; Gilmore et al., 2013; Goedel, Halkitis, Greene, & Duncan, 2016; Gupta et al., 2017; Holloway et al., 2017; Hosek et al., 2017; Parker et al., 2015; Storholm et al., 2017). The lowest rate (27%) was in a study where the majority of participants had a main partner (Castro et al., 2017); with the exception of this study, the CAI range was 40% to 87%.

Five studies, which examined changes in CAI behavior after participants had started PrEP, reported no increase in rates of CAI or changes in condom use (Hojilla et al., 2016; Hosek et al., 2013; Liu et al., 2013; Molina et al., 2015; Parker et al., 2015). However, three studies (2 RCTs, 1 open label) reported increases in the frequency of CAI and, in two studies, CAI was specifically receptive (McCormack et al., 2016; Molina et al., in press; Oldenburg et al., 2017). McCormack et al. (2016)

found that the increase in receptive CAI occurred only in participants who reported more than 10 sexual partners. However, six studies that examined PrEP use over different time frames reported that PrEP initiation did not lead to an increased number of sex partners for the majority of participants (McCormack et al., 2016; Molina et al., 2015; Molina et al., in press; Oldenburg et al., 2017; Parker et al., 2015; Volk et al., 2015). Two U.S. studies found that, following PrEP initiation, 35% to 41% of the sample decreased use of condoms, whilst 3% to 27% reported increased use of condoms (Strauss et al., 2017; Volk et al., 2015).

Four studies reported that PrEP users were more likely to have more sex partners than non-PrEP users (Goedel, Halkitis, Greene, & Duncan 2016; Goedel, Halkitis, Greene, Hickson et al., 2016; Holloway et al., 2017; Okafor, Gorbach, Ragsdale, Quinn, & Shoptaw, 2017). Four studies found that PrEP users were more likely to have sex with partners living with HIV than non-PrEP users (Holloway et al., 2017; Kuhns et al., 2017; Okafor et al., 2017; Taylor et al., 2014). One U.S. study reported that MSM who engaged in CAI with partners living with HIV were five times more likely to use PrEP than MSM who did not have CAI with men living with HIV (Hoots et al., 2016).

The evidence for risk compensation (increases in high-risk sexual behaviors) and number of sexual partners after starting PrEP was mixed. The evidence did indicate that PrEP users may have had more CAI and sex partners than non-PrEP users, including men living with HIV. However, this was expected as CAI and partner numbers were criteria for being offered PrEP.

Sexually Transmitted Infections

Fourteen studies reviewed STIs in MSM who used PrEP. Nine studies

reported an overall STI incidence estimate for PrEP users, which ranged from 20% to 66% (Bien, Patel, Blackstock, & Felsen, 2017; Chan, Mena, et al., 2016; Doblecki-Lewis et al., 2017; Hosek et al., 2017; Liu et al., 2016; Marcus et al., 2016; McCormack et al., 2016; Molina et al., 2015; Volk et al., 2015). The lowest rate (20%) was from a U.S. study with a relatively small number of PrEP users and 66% was from a study of YMSM. Only six studies examined specific STIs, and the majority identified the most common infections as chlamydia and gonorrhea (Daughtridge, Conyngham, Ramirez, & Koenig, 2015; Deutsch et al., 2015; Hosek et al., 2013; McCormack et al., 2016; Molina et al., 2015; Molina et al., in press; Volk et al., 2015). The wide range of STI incidence reflected heterogeneity of study populations, but all found a high STI burden in MSM at high risk of HIV acquisition.

Hoots et al. (2016) found that MSM who had been diagnosed with an STI in the previous year were more likely to use PrEP than MSM who had not had an STI in the previous year, but this finding should be expected, as an STI in the previous year was a clinical indicator for PrEP. Another U.S. study reported that STI diagnosis in the previous year was associated with PrEP use (Holloway et al., 2017). A U.S. cohort study reported that, 1 year after PrEP initiation, diagnosis of urethral gonorrhea and rectal chlamydia increased, but all other STIs/sites remained stable (Marcus et al., 2016). Another U.S. cohort study reported that, following PrEP initiation, overall STI incidence at 6 months was 30% and increased to 50% at 12 months (Volk et al., 2015). Cohort studies were limited by not having control groups to determine if STI increases were directly related to PrEP use. In contrast, two RCTs, which analyzed the efficacy of PrEP, reported that, during study follow-up, PrEP and control groups showed no significant differences in STI rates (McCormack et al., 2016; Molina et al., 2015). The evidence suggests that MSM using PrEP had a

high burden of other STIs, but there was limited evidence to suggest that PrEP use increased or reduced STI incidence.

PrEP Adherence

Eleven studies examined levels of PrEP adherence, using single- or combined-monitoring methods, ranging from self-report to blood tests. Ten studies examined continuous dosing regimens, in which adherence was defined as taking four or more pills per week. Four studies monitored PrEP levels via blood tests and reported that, 24 weeks after staring PrEP, 20% to 84% of the sample had drug levels equivalent to 4 or more pills per week (Hosek et al., 2017; Hosek et al., 2013; Liu et al., 2016; Mayer et al., 2017). Two of these studies reported that, 48 weeks after starting PrEP, 34% to 80% of the sample had adequate drug levels (Hosek et al., 2015; Liu et al., 2016). The studies that reported lower adherence levels of 20% to 55% at week 24, and 34% at week 48, only examined PrEP use in YMSM (Hosek et al., 2015; Hosek et al., 2013). In contrast, the two studies that had non-specific age samples reported an adherence level at week 24 of more than 80% (Liu et al., 2016; Mayer et al., 2017).

Six studies used self-report to monitor PrEP use, in which three reported overall adherence of 80% to 90% (Chan, Mena, et al., 2016; Daughtridge et al., 2015; Liu et al., 2016). A study that examined potential and actual use of PrEP in the cycle of change found that 98% of the sample using PrEP reported taking more than four doses per week (Parsons et al., 2017). Two studies reported that, at 6 months of PrEP use, participants reported taking 20 to 27 daily doses in the previous 30 days (Hosek et al., 2013; Montgomery et al., 2016). In contrast, Storholm et al. (2017) reported that, after using PrEP for 3 months, their sample had taken 5.5 doses a

week on average. Three studies used pill counting as a monitoring mechanism and reported an adherence level of 80% to 92% (Liu et al., 2016; Marcus et al., 2016; Mayer et al., 2017).

Two studies used two or more monitoring strategies and found that an adherence level of more than 80% was consistent between self-report and blood testing (Liu et al., 2016; Mayer et al., 2017). However, Hosek et al. (2013) found that participants reported high adherence levels, but blood monitoring indicated that a small minority had adequate drug levels to evidence effective adherence. Studies showing consistent adherence had generalized MSM samples; inconsistent reporting was found in studies of YMSM, ages 18 to 22.

Only three articles examined episodic PrEP dosing. Recommended dosing in these studies was two pills 2 to 24 hours before sex, a third pill 24 hours after the first dose, and a fourth pill 24 hours later. Two reported that about half fully adhered and a quarter partially adhered to the regimen (Molina et al., 2015; Molina et al., in press). Molina et al. (2015) reported that 28% of their sample used 15 pills per month on average. In contrast, Molina et al. (in press) reported that 70% of their sample had detectable drug levels 6 months after starting PrEP. Sagaon-Teyssier et al. (2016) found that 59% of their sample fully adhered to the dosing schedule; 41% used a sub-optimal dosing regimen. In contrast, Molina et al. (in press) reported that 9% of their sample did not use PrEP consistently at their last sexual encounters. The majority of episodic PrEP users adhered to the regimen, but the evidence was not as strong as for continuous regimens.

Fourteen studies examined biopsychosocial factors that could affect adherence; the majority of evidence came from continuous regimens. Six studies examined patient-related lifestyle factors. Two found that 27% to 47% of participants

forgot to take pills because of busy schedules and 28% to 50% simply forgot to take some doses (Hosek et al., 2017; Hosek et al., 2013). Three studies reported that 27% to 60% of participants didn't take doses when away from home (Gilmore et al., 2013; Hosek et al., 2017; Hosek et al., 2013). Three studies examined elements of substance use; two reported that alcohol use had a negative impact on PrEP adherence (Storholm et al., 2017; Taylor et al., 2014) and two reported that stimulant drugs were related to non-adherence (Oldenburg et al., 2016; Storholm et al., 2017).

A study from Canada examined mental health and substance use in men being processed for initial PrEP consultation and reported problematic alcohol use (38%), problematic drug use (35%), and/or a mental health diagnosis (41%; Tan, Leon-Carlyle, Mills, Moses, & Carvalhal, 2016). One study reported that symptoms of depression in participants contributed to missed doses of PrEP (Taylor et al., 2014). In contrast, five studies stated that a fundamental reason to use PrEP was to remove the fear of contracting HIV (Hojilla et al., 2016; Holloway et al., 2017; Hosek et al., 2013; Malone et al., 2017; Mimiaga et al., 2014). Overall, mixed factors were related to individual PrEP user adherence.

Five studies examined social and economic factors and reported that participants had a fear of being stigmatized by social supports if they knew the participant was on PrEP (Arnold et al., 2017; Collins et al., 2017; Hosek et al., 2017; Storholm et al., 2017; Taylor et al., 2014). One study reported fear of being judged as promiscuous by community peers (Collins et al., 2017). Storholm et al. (2017) stated that 10% of their sample had experienced stigma from other gay men because of using PrEP. In contrast, Hosek et al. (2017) reported that only 2.5% of their sample had missed doses because they did not want others to know they were taking PrEP.

Three U.S. studies reported that lack of affordable health care was a barrier for some men (Chan, Mena, et al., 2016; Doblecki-Lewis et al., 2017; Taylor et al., 2014). Three studies reported that some of participants had reservations about discussing PrEP use with health care providers for fear of stigma associated with risky sexual behavior and HIV medication (Collins et al., 2017; Eaton et al., 2017; Taylor et al., 2014). The evidence indicated that fear of stigma from peers, health care providers, and health care barriers impacted PrEP uptake, but evidence was limited related to its influence on PrEP adherence.

Five studies examined the impact of side effects on PrEP adherence. Three reported that up to 11% of their samples experienced side effects when taking PrEP (Liu et al., 2016; McCormack et al., 2016; Molina et al., in press). McCormack et al. (2016) reported that 8% of their sample missed doses due to side effects, most commonly nausea and headache. A U.S. study of YMSM reported that 4.5% of the sample intentionally missed doses to avoid side effects (Hosek et al., 2017). In contrast, Arnold et al. (2017), in a small sample, found a majority of participants had no side effects from PrEP and only 2 missed doses because of potential side effects. Overall, the evidence suggests that adherence was affected by side effects in a minority of PrEP users, but particularly in YMSM.

Six studies examined factors that facilitated optimal adherence to PrEP. Three reported an established daily routine as one of the most effective facilitators for adherence (Gilmore et al., 2013; Parker et al., 2015; Taylor et al., 2014); two found that being on other medications facilitated daily doses of PrEP (Gilmore et al., 2013; Taylor et al., 2014). Six studies examined adherence prompts and props: three studies reported the use of prompts (e.g., daily texts, alarms) improved adherence (Parker et al., 2015; Storholm et al., 2017; Taylor et al., 2014) and three found that

some PrEP users found pill boxes useful (Gilmore et al., 2013; Parker et al., 2015; Storholm et al., 2017), but Gilmore et al. (2013) also reported that some participants did not find pill boxes helpful.

Sagaon-Teyssier et al. (2016) found that PrEP, in combination with other HIV prevention strategies, promoted adherence to dosing regimens, and Raifman et al. (2017) reported that a brief PrEP education intervention resulted in a 150% increase in PrEP use compared to PrEP awareness and previous PrEP use prior to education. Another facilitator was related by users who engaged in high-risk sexual behavior and viewed PrEP as a “necessity” to reduce HIV risk. The overall evidence did not indicate that one specific factor promoted optimal adherence, but adherence prompts, structured adherence support, and education might be beneficial.

Discussion

To our knowledge, this was the first systematic review to analyze MSM PrEP use and medication adherence in high-income countries. Other literature reviews (Huang et al., 2018; Pinto, Berringer, Melendez, & Mmeje, 2018; Sidebottom, Ekstrom, & Stromdahl, 2018; Traeger et al., 2018; Young & McDaid, 2014) examined PrEP efficacy, sexual behavior, and medication adherence, but did not provide in-depth behavioral analyses of PrEP use among MSM.

We used the ABC framework (Meaden et al., 2014) to structure and synthesize evidence of behavioral processes in MSM PrEP use. The main strength of this approach was that it allowed a wide range of complex evidence to be synthesized into a three-stage process. Sexual behavior was congruent with the three ABC stages. Men who initiated PrEP used it as an additional HIV risk reduction strategy and engaged in varied high-risk sexual behaviors (Antecedents). Following

PrEP initiation, users were likely to continue high-risk sexual activity (Behaviors) in comparison to non-users. There was mixed evidence on whether PrEP initiation was substantially associated with risk compensation, but some MSM subgroups saw PrEP as an opportunity to reduce consistent condom use (Consequences).

The evidence for changes in sexual behavior (risk compensation) following PrEP use is complex. As in a systematic review of PrEP efficacy (Huang et al., 2018), we did not find consistent increases in sex partners or CAI and there was a lack of evidence to indicate an increase in STI diagnoses. However, another systematic review concluded that PrEP use was associated with increased sex without condoms and diagnoses of STIs, particularly a significant increase in rectal chlamydia (Traeger et al., 2018).

Two studies in our review suggested that there were increases in higher risk behaviors in a subgroup of PrEP users. Overall, this reflected limitations in assessing changes in sexual behavior in observational studies. First, PrEP users were likely to engage in high-risk sexual activity prior to PrEP initiation and to continue those behaviors. Second, before and after observational studies cannot control for secular change and social desirability biases in reporting high-risk behaviors on or off PrEP. Further research is required to investigate if risk compensation and STI diagnosis are associated with PrEP uptake.

We found that a minority (<10%) of MSM were using PrEP, but this was with limitations in non-representative samples with clear geographic heterogeneity in PrEP use and mixed quality. There was a lack of substantive data on the population level of MSM PrEP use in high-income countries and studies examining prevalence estimates were limited by heterogenous sampling.

A systematic review of PrEP implementation in the United States found health

care system barriers affecting uptake, including PrEP-related stigma and financial capability, which was non-equitable across races/ethnicities (Pinto et al., 2018). This study was congruent with findings in our review, but we found challenges when engaging young and racial/ethnic minority MSM in PrEP uptake and adherence. The barriers for YMSM are of concern if they have limited financial capability to pay for PrEP and if the health care system limits PrEP provision. There is a need to systematically monitor HIV incidence, PrEP uptake, and retention disaggregated by age and race/ethnicity in different geographic settings. This should be coupled with well-designed MSM studies to ensure equitable access to PrEP.

A systematic review found that MSM PrEP users of continuous and episodic dosing regimens had high levels of medication adherence (Sidebottom et al., 2018), which was consistent with our findings. However, a limited evidence base suggested that substance users and those with mental health diagnoses may have higher levels of non-adherence. Substance use by MSM is particularly important, as gay and bisexual men are three times more likely to use illicit drugs than heterosexuals (Office for National Statistics, 2014). In particular, there are growing concerns about MSM who combine drugs with sex (Maxwell, Shahmanesh, & Gafos, 2019).

Chemsex is the intentional use of psychoactive drugs to facilitate or enhance sex. A systematic review reported that up to 13% of MSM engaged in chemsex, which often results in high rates of CAI, multiple sex partners, partners of unknown HIV status, and injecting drug use (Maxwell et al., 2019). In a study of intended PrEP use, chemsex participants reported their drug use would negatively impact PrEP adherence and choice of dosing regimen would depend on frequency of drug use (Closson, Mitty, Malone, Mayer, & Mimiaga, 2018). The use of PrEP by substance users may be a viable HIV risk reduction strategy, but further research is required to

examine PrEP use in substance users and the impact on adherence. Overall, further investigations are needed to explore PrEP medication adherence in specific MSM populations.

To overcome barriers to adherence, it is important to examine what influences non-adherence. A systematic review of non-PrEP medication adherence in uninfected MSM reported that about 80% adhered to their medications, but barriers included forgetting, being away from home, and changes in daily routine (Liu et al., 2014); their findings were consistent with our study, which found high adherence levels, but that daily logistics contributed to non-adherence.

A specific influence for PrEP adherence was the user's perception of stigma from community peers and health care providers. A systematic review from the United States reported that potential health care provider stigma related to HIV, PrEP, and same-sex behavior could keep high-risk individuals from starting PrEP (Pinto et al., 2018). Our findings were similar to Liu et al. (2014), who found that an established daily routine and pill boxes could promote adherence. However, limited research has examined facilitators of PrEP adherence in high-risk MSM.

Strengths and Limitations

Our review was strengthened by a clear search protocol and well-established frameworks to structure and analyze the wide array of evidence. Use of the ABC framework provided a clear and simple model to understand behavioral processes of MSM PrEP use. Our review was limited by a lack of clear sampling frameworks and the heterogenous nature of samples across studies. In addition, we only included studies that were fully published in English.

Research Recommendations

To better understand PrEP use by MSM in high-income countries, research in the following areas is recommended: (a) Examine prevalence estimates and patterns of PrEP use by age and race/ethnicity in different countries to ensure equitable access; (b) Examine changes in sexual behavior and diagnosis of STIs after PrEP initiation; and (c) Explore barriers and facilitators for PrEP uptake and adherence in high-risk MSM. As PrEP is an effective HIV risk reduction strategy and increasingly available in high-income countries, research in these areas would provide a foundation for evidence-based policy.

Conclusion

A minority of MSM in high-income countries use PrEP, but it appears to have increased in line with increasing availability. MSM who use PrEP were more often those who engaged in high-risk sexual behavior, but some users changed sexual behavior as a result of starting PrEP. MSM had high medication adherence levels but specific high-risk groups had a lower uptake, were less adherent, and might have been at higher risk of HIV acquisition. As PrEP is increasingly available, it is important to understand what facilitates PrEP uptake and supports adherence for MSM at higher risk of acquiring HIV. Finally, there is a specific need for research to explore episodic use of PrEP.

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Key Considerations

- PrEP users engage in high-risk sexual behaviors and PrEP initiation potentially means some users will risk compensate.
- MSM have high PrEP adherence levels, but younger men, substance users, and those with a mental health diagnosis have higher non-adherence levels.
- Barriers to PrEP uptake and adherence include stigma, side-effects, cost, daily logistics, and forgetting.
- Facilitators that promote PrEP adherence include availability, daily routine, daily texts/alarms, pill boxes, and education.

Table 1

ABC Analysis of PrEP use and Medication Adherence

Antecedent	Behavior	Consequence
• Socio-demographic characteristics • Reasons/motivators for PrEP initiation	• Prevalence • Sexual behavior • STI rates • PrEP adherence levels • Influences on PrEP adherence	• STI diagnosis • Changes in sexual behavior *(risk compensation)*

Note. ABC = Antecedent, Behavior, Consequence; PrEP = pre-exposure prophylaxis;

STI = sexually transmitted infection.

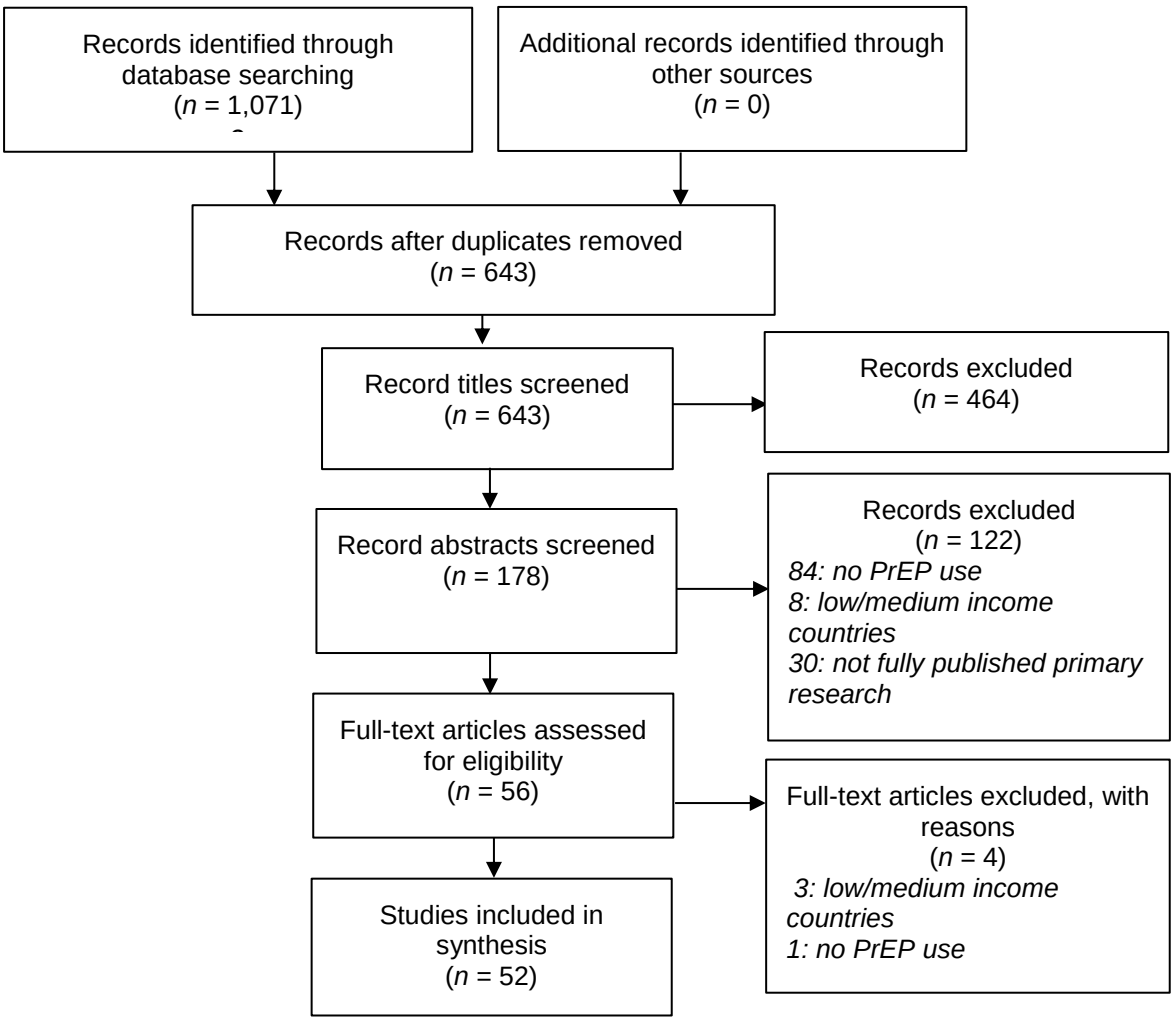

Figure 1. Study selection process.

Note. PrEP = pre-exposure prophylaxis. PRISMA flowchart from Moher, Liberati, Tetzlaff, & Altman, 2009.

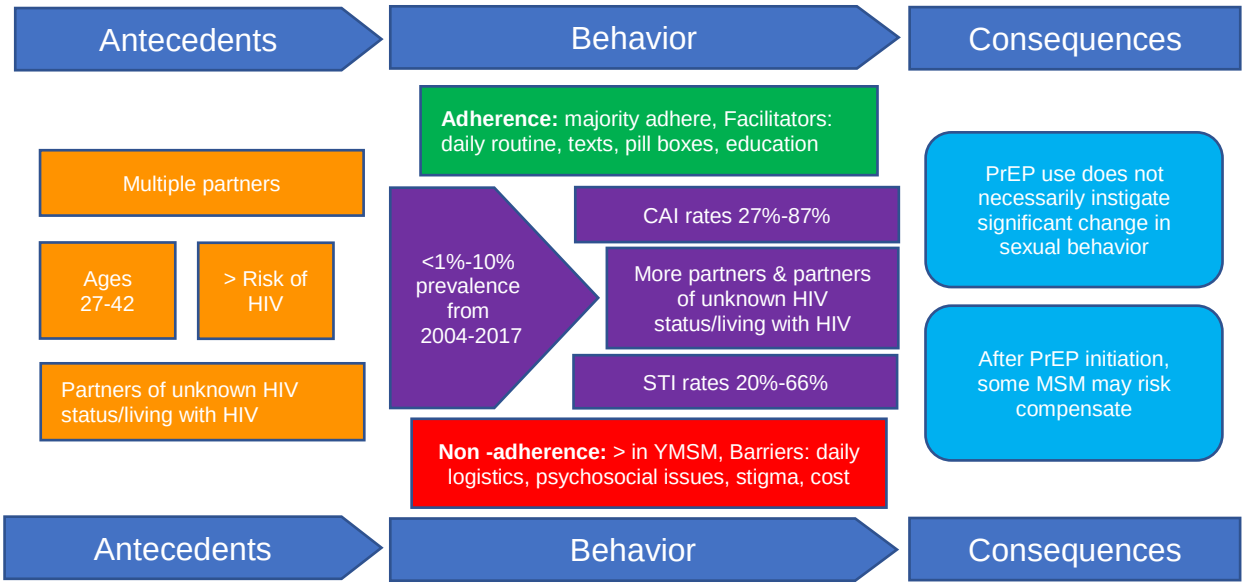

Figure 2. ABC summary of findings.

Note. ABC = Antecedent, Behavior, Consequence; PrEP = pre-exposure prophylaxis; CAI = condomless anal intercourse; MSM = men who have sex with men; YMSM = young men who have sex with men.