



Barriers to the Wider Use of Pre-exposure Prophylaxis in the United States: A Narrative Review

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ABSTRACT

Antiretroviral pre-exposure prophylaxis (PrEP) to prevent HIV transmission was first approved by the US Food and Drug Administration in 2012. Despite correlations of decreases in new HIV infections being greatest where PrEP has been deployed, the uptake of PrEP is lagging, particularly among populations with disproportionate HIV burden. This narrative review seeks to identify individual and systemic barriers to PrEP usage in the USA. A comprehensive search of recent literature uncovered a complex array of structural, social, clinical, and behavioral barriers, including knowledge/awareness of PrEP, perception of HIV risk, stigma from healthcare providers or family/partners/friends, distrust of healthcare providers/systems, access to PrEP, costs of PrEP, and concerns around PrEP

side effects/medication interactions. Importantly, these barriers may have different effects on specific populations at risk. The full potential of PrEP for HIV prevention will not be realized until these issues are addressed. Strategies to achieve this goal should include educational interventions, innovative approaches to delivery of HIV care, financial support, and destigmatization of PrEP and PrEP users. Until then, PrEP uptake will continue to be suboptimal, particularly among those who need it most.

PLAIN LANGUAGE SUMMARY

Pre-exposure prophylaxis (PrEP) is a way of preventing HIV. By taking a daily pill, which contains two medicines, HIV can be stopped before it causes an infection. PrEP is prescribed for people at risk of HIV infection. However, many people who are at risk do not use PrEP. We explored the reasons for this. We found that many individuals at risk had not heard of PrEP, so would be unable to ask their doctors for it. Even among healthcare providers themselves, some were not aware of PrEP or how it should be used. For individuals who have heard of PrEP, unfortunately a stigma remains around HIV that deters some people from seeking the treatment. Furthermore, many individuals at

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risk have experienced bias at the hands of healthcare providers, deepening distrust of the medical establishment. Many individuals at risk also experience poverty and although there are multiple financial assistance options for PrEP, these can be difficult to access without support. Public education and training of healthcare providers may address many of the barriers we found, but deep-rooted issues such as racism and bias will require significant changes within the healthcare system.

Keywords: Access; Barriers; Distrust; Emtricitabine; Implementation; Prevention; Pre-exposure prophylaxis; Stigma; Tenofovir alafenamide; Tenofovir disoproxil fumarate

Key Summary Points

Antiretroviral pre-exposure prophylaxis (PrEP) reduces HIV transmission, but barriers to PrEP access limit uptake in the USA.

Awareness of PrEP remains low in populations at risk and is inadequate in some healthcare provider settings, requiring educational initiatives.

Low perception of HIV risk among individuals and healthcare providers limits PrEP uptake, alongside lack of access to appropriate, unbiased medical care.

Financial and social stigma barriers also reduce PrEP uptake, although legal changes to PrEP coverage by insurance providers and social media interventions may provide opportunities to overcome these barriers.

INTRODUCTION

The antiretroviral combination of emtricitabine and tenofovir disoproxil fumarate (Truvada®;

F/TDF) was the first medication approved by the US Food and Drug Administration in 2012 for use as HIV pre-exposure prophylaxis (PrEP) to prevent HIV acquisition, based on several pivotal trials [1–3]. Since then, PrEP medications have been shown to be effective at preventing HIV transmission in those at greatest risk of acquisition. A retrospective analysis of the National HIV Surveillance System and national pharmacy data showed an independent and significant association between F/TDF PrEP use and a decline in the number of new HIV infections diagnosed in the USA from 2012 to 2016 in communities where it was most widely used [4]. Over this period, PrEP use increased from 7.0 to 68.5 per 1000 persons for whom it was indicated (estimated annual percent change (EAPC) + 78.0, confidence interval (CI) + 77.3, 78.7%), while the rate of new HIV diagnoses among the general population decreased significantly from 15.7 to 14.5 per 100,000 persons (EAPC – 1.6, CI – 1.9, – 1.3). In states with the highest PrEP use (11% average prevalence among individuals for whom PrEP is indicated), the pooled EAPC of HIV diagnoses was – 4.7%, whereas the EAPC of HIV diagnoses was + 0.9% in states with the lowest PrEP use (3% average prevalence among PrEP-indicated individuals). The observed association of PrEP with decreasing HIV incidence remained significant after controlling for state-specific levels of viral suppression among HIV-positive individuals.

Despite the effectiveness of PrEP in the prevention of HIV transmission, there remain challenges, reflected by low levels of utilization in the USA. As of the third quarter of 2019, an estimated 224,000 people in the USA received a prescription for HIV PrEP (Gilead Sciences, data on file), a fraction of the 1.1 million Americans estimated to have indications for PrEP (data as of 2015) [5, 6]. The lack of uptake is especially low among populations disproportionately affected by HIV.

For example, Black and Latinx individuals (who represented 69% of new HIV diagnoses in 2017) comprised only 24% of PrEP users in 2016 [7, 8]. PrEP uptake may also be insufficient in people who inject drugs (PWID). A survey of primary care physicians showed over one-quarter had low willingness to prescribe PrEP to

PWID, despite some PWIDs having a substantial risk for HIV acquisition [9]. Cisgender women at risk of HIV also have relatively low PrEP uptake. Based on available commercial US pharmacy data, the EAPC between 2012 and 2017 was a 5% increase for women starting PrEP, compared with a 68% increase among men [5]. Furthermore, a Centers for Disease Control (CDC) analysis of 2016 prescription data found that only 2% of women for whom PrEP was indicated were using it [7]. This reflects an inequality in PrEP use for women relative to their need, since more than a quarter of new HIV infections (in 2016) occurred in women [5].

Age may be a factor in PrEP uptake; young individuals at risk have lower levels of PrEP use relative to their need [10, 11]. In an analysis of 2017 prescription-level data, PrEP use in those under 24 years of age was 15.2 per 100,000 persons, with a PrEP-to-need ratio (PnR; ratio of PrEP users to new HIV diagnoses) of 0.9. In comparison, among those aged 24–35 years, PrEP use was 61.5 per 100,000 persons, and the PnR was 2.0 [11]. Finally, geography may also contribute to disparity in rates of PrEP use. For instance, although men and women in the South accounted for 52% of US HIV diagnoses in 2017, only 27% of PrEP users were in the South (from 2016 data) [7, 12].

Importantly, there appears to be a mismatch between individual risk/risk perception and PrEP uptake. A Seattle survey of men who have sex with men (MSM) and transgender individuals (men and women) who have sex with men showed that only 3% of participants had ever used PrEP, despite nearly all having heard of PrEP and having health insurance [13]. Similarly, in a 2019 survey of transgender men, although 55.2% of respondents had an indication for PrEP, only 21.8% reported current PrEP use [14]. Additionally, an analysis of over 400 MSM in Los Angeles demonstrated that knowledge of PrEP increased from 39% to 82% from 2011 to 2014, but actual PrEP use rose from no use to only 8% across the same period [15, 16].

In summary, poor PrEP uptake among individuals for whom it is indicated is a substantial

problem in the USA, affecting diverse groups. Understanding barriers to PrEP use is paramount in ensuring its effective implementation, particularly among populations with disproportionate and/or increasing rates of HIV acquisition. In this narrative review, we aim to assess and characterize barriers to PrEP use in the USA. We will examine barriers for both individuals at risk and providers, exploring which barriers are common to most populations and which are highlighted in specific populations.

SEARCHES

We assessed peer-reviewed papers and conference abstracts to identify barriers to PrEP uptake in the USA among those at risk for HIV by searching PubMed, International AIDS Conference 2019, and Conference on Retroviruses and Opportunistic Infections 2019 abstracts, using the terms “PrEP OR pre-exposure prophylaxis OR pre-exposure prophylaxis” AND “HIV” AND “clinical trial OR classical article OR clinical study OR comparative study OR meta-analysis OR multicenter study OR observational study OR qualitative research OR barriers”. As this field is rapidly evolving, we focused on articles from 2016 onwards. Key themes were identified from the initial search: knowledge/awareness of PrEP; perception of HIV risk; social stigma; provider bias and distrust of healthcare providers/systems; lack of access to medical care; lack of access to (or awareness of) financial assistance options; and PrEP side effects and medication interaction concerns (Table 1). Each of the identified barrier categories was reviewed with consideration of individual behavioral and sociodemographic factors, as well as healthcare provider/systemic factors. Other relevant references were identified for each category either from the bibliography of original articles or by carrying out additional PubMed searches during manuscript development on “PrEP OR pre-exposure prophylaxis OR pre-exposure prophylaxis” AND “HIV” AND (knowledge OR

Table 1 Summary of key barriers to PrEP uptake as identified in the recent literature and potential approaches to removing barriers to PrEP

Key barriers	Potential approaches to removing barriers
Awareness of PrEP	Patient and provider education Better communication between providers
HIV risk perception	Patient and provider education
Stigma	Improved cultural humility (via education and advocacy) Improved communication and understanding between patient and provider
Provider bias and distrust of healthcare system	Patient and provider education Addressing systemic entrenched bias (via education, advocacy, and recruitment of more Black, Latinx, and LGBTQ healthcare professionals)
Access to medical care	Patient and provider education Extending access to PrEP (e.g., substance use clinics, emergency rooms, pharmacies, correctional institutions, etc.) Leveraging technology to improve access (e.g., telemedicine) Addressing competing priorities (e.g., food, shelter, safety, other healthcare, childcare)
Lack of access to financial assistance	Help for patients in navigating financial aid options
Side effects	Patient and provider education

HIV human immunodeficiency virus, *LGBTQ* lesbian, gay, bisexual, transgender, and queer, *PrEP* pre-exposure prophylaxis

awareness OR risk perception OR stigma OR bias OR distrust OR access OR cost OR side effects OR interaction). This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

AWARENESS AND KNOWLEDGE AS A BARRIER TO PREP UPTAKE

Before any other factors influencing PrEP uptake come into play, both individuals at risk and healthcare providers need to be aware of the existence of PrEP as a preventive option. Nationally, in the general population, awareness of PrEP is low. In a survey of 19,806 adults in the USA (general public) between 2009 and

2014, only 6.5% reported awareness of PrEP [17]. More recent national data are not available, but smaller studies suggest that general awareness remains low. A 2018 study of the North Carolina general public ($N = 409$) found that only 9% had heard of PrEP [18]; a 2018 Southern Arizona study ($N = 500$) noted that only 20% of individuals surveyed at public health department clinics (which provided family planning and sexually transmitted infection testing/treatment) were aware of PrEP [19].

In populations at high risk for HIV acquisition, PrEP awareness varies and study findings are often contradictory. For example, relatively high knowledge/awareness of PrEP among racially and ethnically diverse populations of MSM, transgender women, and transgender

Table 2 Summary of recent data indicating that knowledge/awareness is a barrier to PrEP uptake among individuals at risk of HIV

Demographic variable	Study design	Summary of data	References
Sexual orientation	Survey of Black men and TGW who have sex with men attending Black Gay Pride events in five US cities ($N = 1274$) ^a	Only 39% of participants were aware of PrEP. PrEP awareness among TGW was 4.7%	[155]
	Survey of substance-using Black MSM and TGW in New York City ($N = 1673$) ^b	Only 18.2% of participants were aware of PrEP	[156]
Gender ^{a,b}	Survey of women visiting safety net family planning clinics in Atlanta ($N = 500$), of whom 47% were aged ≤ 28 years, 69% Black, and 12% Hispanic	Only 19% of participants knew about PrEP before their visit	[157]
	Assessment of women enrolled in an HIV study at Southern US sites ($N = 225$), the majority of whom were Black (83%)	Of the 72 participants who were PrEP-eligible, only 11% had previously heard of PrEP	[158]
Race/ethnicity ^{c,d}	Focus groups and interview of HIV-negative cis women visiting an STI clinic or emergency department in Chicago ($N = 370$), the majority of whom were Black (83%) ^d	Only 30% of participants had heard of PrEP before the survey. The only factor associated with hearing about PrEP was knowing someone on PrEP	[159]
	Cross-sectional survey of HIV-negative cis women involved in the criminal justice system ($N = 125$)	Only 25% of participants were aware of PrEP	[37]
Race/ethnicity ^{c,d}	Survey of individuals attending family planning and sexual health clinics in Arizona, the majority of whom were women (65%)	Women had lower prior awareness of PrEP than men	[19]
	Survey of TGM who have sex with cis men ($N = 857$)	84.1% of participants had heard of PrEP	[160]
Race/ethnicity ^{c,d}	Survey of a Northern California consortium of individuals with recently acquired HIV ($N = 122$), the majority of whom were MSM (84%) and of minority racial/ethnic background (64%)	A lack of PrEP awareness was noted in 69% of Black participants	[161]
	Survey of Black individuals in the USA ($N = 855$)	Only 15% of all participants were aware of PrEP, with awareness of 20% among individuals at high risk	[162]
Race/ethnicity ^{c,d}	Analysis of PrEP awareness among HIV-negative MSM overall and by race using National HIV Behavioral Surveillance data from 20 cities in the USA	PrEP awareness increased overall from 59% to 90% between 2014 and 2017, but was lower among Black and Hispanic men (both 85%) compared with White men (94%)	[163]

Table 2 continued

Demographic variable	Study design	Summary of data	References
History of substance abuse ^b	Interview of clinical and social service providers from Massachusetts and Rhode Island (<i>N</i> = 18) who work with PWID	Informants expressed concerns relating to low PrEP knowledge among PWID	[83]
Age	Interview of HIV-negative PWID in Boston and Providence (<i>N</i> = 33)	Low PrEP knowledge was identified as an individual-level barrier to PrEP use	[84]
	Survey of a Northern California consortium of individuals with recently acquired HIV (<i>N</i> = 122), the majority of whom were MSM (84%) and of minority racial/ethnic background (64%)	Lack of PrEP awareness was more prominent among individuals aged < 25 years (88%) than those aged 25–34 years (39%)	[161]
	Data from HIV-negative TGW aged 16–29 years enrolled in Project LifeSkills during 2012–2015 (<i>N</i> = 230), the majority of whom were of color (67%)	Younger age (21–25 versus 26–29 years) was associated with lower PrEP acceptability	[164]
	Survey and interview of young adults experiencing homelessness in Houston (<i>N</i> = 30) or Los Angeles (<i>N</i> = 15)	Low or no prior knowledge of PrEP was reported by 68% of participants	[165]
	Survey of young (age 18–30 years) HIV-positive minorities in South Texas (<i>N</i> = 92)	Only 45% of participants knew about PrEP at the time of their diagnosis	[166]
Geographic location	Focus groups of gay, bisexual, and other MSM in Boston, Massachusetts and Jackson, Mississippi (<i>N</i> = 35)	Boston focus group participants were more likely to be aware of the concept of taking a pill to prevent HIV infection (73%) than Jackson participants (29%)	[167]
	Interview of current and potential PrEP users in Alabama (<i>N</i> = 44)	Participants had a lack of PrEP awareness	[76]

cis transgender, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *PrEP* pre-exposure prophylaxis, *PWID* people who inject drugs, *STI* sexually transmitted infection, *TGW* transgender men, *TGW* transgender women

^a Please see study of Black men and TGW who have sex with men in the “Sexual orientation” category, also applicable here [155]

^b Please see study of substance-using Black MSM and TGW “Sexual orientation” category, also applicable here [156]

^c Please see study of women in the “Gender” category, also applicable here [158]

^d Please see study of cis women in the “Gender” category, also applicable here [159]

Table 3 Summary of recent studies about PrEP awareness and knowledge among healthcare professionals/providers

Study participants	Study methods	Summary of key data	References
US nurse practitioners ($N = 271$)	Cross-sectional survey of American annual conference attendees; presented in 2019	60.1% reported no prior PrEP training or education; 62.4% reported never starting a conversation about PrEP; Half reported being ‘confident’ in discussing PrEP with an individual, monitoring PrEP side effects, or testing PrEP patients for HIV	[25]
Physicians (adolescent medicine/family practice/internal medicine/pediatrics/obstetrics and gynecology) providing primary care to adolescents aged 13–21 years ($N = 38$)	Individual, in-depth, semi-structured interviews	37% reported being somewhat or very familiar with PrEP; perceived benefits of prescribing PrEP included decreased HIV acquisition, and improved awareness of HIV risk among recipients	[31]
Internal medicine trainees at a medium-sized internal medicine program ($N = 48$)	PrEP-focused educational intervention with pre-intervention and post-intervention surveys	Pre-intervention: 22% of trainees were unaware of PrEP, 78% believed PrEP was effective, 66% believed it was safe, and 62% had fair/poor awareness of side effects Post-intervention: 94% believed PrEP was effective and 92% believed PrEP was safe	[98]
Clinical and social service providers who work with PWID in small cities and towns in Massachusetts and Rhode Island ($N = 18$)	Semi-structured qualitative interviews; presented in 2019	Interviewees viewed PrEP as a promising but underutilized HIV prevention strategy. Interviewees also reported limited confidence among staff delivering PrEP	[83]
First-year health professions students and interdisciplinary care teams at a health department in Illinois ($N = 11$)	Mixed-methodology assessment of a service-learning project to compile a training module (by health professions students), presented to interdisciplinary care teams	Students and care teams underinformed about PrEP had self-reported increased awareness and confidence in identifying individuals at risk for HIV infection after training intervention	[168]

Table 3 continued

Study participants	Study methods	Summary of key data	References
Healthcare providers (including infectious disease consultants, family/general practitioners, obstetrics/gynecology specialists, internist, and physician assistant) in Florida ($N = 12$)	25-item questionnaire, conducted between January and March 2017	66.7% correctly defined PrEP; 58.3% had read the CDC's PrEP clinical practice guidelines; 41.7% were able to correctly identify PrEP prescribing recommendations	[26]

CDC Centers for Disease Control, *HIV* human immunodeficiency virus, *PrEP* pre-exposure prophylaxis, *PWID* people who inject drugs

men was noted in some studies (Table 2), while others suggest low awareness in these populations (Table 2). However, several studies have more consistently demonstrated lack of awareness of PrEP among other populations at risk of HIV acquisition, including Black MSM, PWID, younger individuals, and communities in the Deep South (Table 2). Even among individuals aware of PrEP, limited knowledge about PrEP (i.e., if they have questions or concerns about it) can prevent PrEP initiation [20].

Lack of PrEP awareness has also been observed among people living with HIV, as was reported for 66% of participants ($N = 137$) surveyed in a Miami public hospital [21]. This is concerning, as these people living with HIV would be unable to advise their partners about PrEP [21]. In that same study, once they knew about PrEP, 86.0% of respondents reported that they would encourage their partners to use it [21].

Knowledge and awareness of PrEP among healthcare providers are also crucial for successful implementation [22] and can directly impact prescribing rates. In a study of local health departments in North Carolina, lack of PrEP awareness and knowledge among health department staff was cited as one of the most common reasons for not prescribing or referring individuals for PrEP [23].

While one 2018 study of New Jersey healthcare workers (including administrators, prescribers, social workers, and nurses) demonstrated a high level of PrEP awareness, at 91% [24], other studies suggest inadequate knowledge or awareness among some

healthcare professionals/providers (Table 3). For example, 60% of 271 US nurse practitioners reported no prior PrEP training or education [25], while 58.3% of 12 Florida healthcare providers had read the CDC's PrEP clinical practice guidelines, and only 41.7% could identify correct PrEP prescribing recommendations [26].

There are clear differences in awareness and knowledge within the healthcare professions. Only 65% of licensed medical providers surveyed in Washington State in 2016 ($N = 735$) had heard of PrEP, with younger healthcare professionals and those with a medical degree more likely to be aware of PrEP than older healthcare professionals and those with other training backgrounds [27]. There was also a disparity in awareness according to specialty; all infectious disease specialists surveyed had heard of PrEP, compared with around three-quarters of board-certified family medicine and internal medicine practitioners and around half of obstetrics/gynecology and pediatric practitioners [27]. Similarly, in a study of 53 family physicians, 71% had no/limited knowledge of PrEP treatment guidelines [28].

This disparity in awareness and knowledge between different healthcare professionals is important when considering the setting in which PrEP should be prescribed. Primary care doctors and generalists often consider PrEP to be an issue for HIV specialists [29, 30]. However, while infectious diseases specialists have knowledge of PrEP and the most experience in HIV care, they usually do not provide care for HIV-negative individuals who may benefit from PrEP; in fact, primary care physicians are more

Table 4 Summary of recent data indicating that perception of HIV risk is a barrier to PrEP uptake among individuals at risk of HIV

Demographic variable	Study design	Summary of data	References
Sexual orientation	Survey of a Northern California consortium of individuals with recently acquired HIV ($N = 122$), the majority of whom were MSM (84%) and of minority racial/ethnic background (64%)	Among participants who were aware of PrEP, a barrier to use was perceived as low risk for HIV by 24%	[169]
	Baseline survey for a randomized controlled trial of MSM ($N = 171$)	HIV risk was underestimated by 38% of participants; the most common reason for not using PrEP was low perception of own HIV risk	[169]
	MSM diagnosed with rectal gonorrhoea or chlamydia at an STI clinic ($N = 410$)	Patients who considered themselves to be at medium/high HIV risk were significantly more likely to be interested in PrEP versus those who perceived themselves to be at low/no risk	[170]
	Baseline assessment of a subset of HIV-negative MSM indicating a casual sexual partner in the prior 3 months ($N = 553$) from the ‘M ³ ’ study	Being drunk/buzzed on alcohol during sex was associated with no PrEP use	[171]
Gender	Survey of women attending urban obstetrics and gynecology clinics in Louisiana ($N = 144$), the majority of whom were Black (62%)	Risk of HIV acquisition was estimated to be low by 85% of participants; only 38% of the population were interested in PrEP	[172]
	Focus groups and interview of HIV-negative cis women visiting an STI clinic or emergency department in Chicago ($N = 370$), the majority of whom were Black (83%)	Participants had low perceived HIV risk (90% low/no risk). Factors associated with starting PrEP included being Latina, recent STI, more concern over HIV, and a higher belief in PrEP effectiveness	[159]
	Interview of women from six cities in the USA ($N = 89$)	Few HIV-negative women expressed an interest in PrEP because they did not consider themselves as at risk for HIV	[173]
	Cross-sectional survey of HIV-negative cis women involved in the criminal justice system ($N = 125$)	Only 17% of PrEP-eligible participants perceived themselves to be at risk for HIV	[37]
	Interview of women experiencing intimate partner violence ($N = 26$)	Potential barriers to PrEP use included low risk perception	[35]
	Philadelphia residents undergoing rapid HIV testing (90% Black) ($N = 5606$)	Investigators categorized 71.6% of men and 60% of women as moderate/high risk; only 56.8% of men and 8.3% of women perceived themselves to be high/moderate risk	[34]

Table 4 continued

Demographic variable	Study design	Summary of data	References
Race/ethnicity	Survey of Black individuals in the USA (<i>N</i> = 855)	Among individuals at high risk, self-perceived risk was low in 65% and only 35% would be willing to use PrEP. Those who saw a healthcare provider less frequently were less willing to use PrEP	[162]
	Survey of individuals undergoing rapid HIV testing in Philadelphia (<i>N</i> = 5606), the majority of whom were Black (90%)	A large proportion of individuals at moderate or high risk for HIV infection did not perceive themselves to be at high risk	[34]
History of substance abuse	Interview of HIV-negative PWID in Boston and Providence (<i>N</i> = 33)	Individual-level barriers to PrEP use included limited HIV risk perception	[84]
	Interview of clinical and social service providers from Massachusetts and Rhode Island (<i>N</i> = 18) who work with PWID	Informants expressed concerns relating to low HIV risk perception among PWID	[83]
Age	Survey and interview of young adults experiencing homelessness in Houston (<i>N</i> = 30) or Los Angeles (<i>N</i> = 15)	Low perceived HIV risk was identified as a barrier to PrEP use	[165]

cis cisgender, *HIV* human immunodeficiency virus, *MSSM* men who have sex with men, *PrEP* pre-exposure prophylaxis, *PWID* people who inject drugs, *STI* sexually transmitted infection

likely to come into contact with such individuals [29, 30]. This creates a “purview paradox” in which each group of healthcare professionals believes that the other is best equipped to provide PrEP [29, 30]. One study interviewed 30 healthcare professionals, including 17 providers who worked in a setting specializing in the care of HIV-positive individuals, on topics including who should be responsible for prescribing PrEP [29]. Both HIV specialists and primary care providers thought that primary care settings were a good site for provision of PrEP, as this is where people at high risk for HIV could be identified. However, there were concerns about a lack of specialist knowledge and bias in the primary care setting, with one HIV specialist stating about primary care: “They have minimal knowledge, and even though they may be treating some people, have probably some prejudice, or at least ambivalence.” It was felt that more training would be needed for primary care settings to offer PrEP.

Specific knowledge about PrEP medication, particularly how they work and the potential side effects, have also been highlighted as critical aspects for provision of PrEP by healthcare professionals [29]. Reluctance to prescribe PrEP may stem from provider misconceptions, such as concern that poor adherence may result in development of resistance [24, 31] despite the fact that clinical evidence to date suggests that HIV drug resistance with PrEP use rarely occurs [32, 33].

LOW PERCEPTION OF HIV RISK AS A BARRIER TO PREP UPTAKE

Some individuals who would be considered, by objective risk assessment, to be at risk for HIV perceive their own risk to be low. This can create another potential barrier to PrEP uptake, albeit with some conflicting evidence. One study has shown that some HIV-negative individuals at risk of infection (including MSM and PWID) perceive themselves to be at risk, are aware of PrEP, and show greater interest in using it than those without these risk factors [19]. However, many other studies have repor-

ted several demographic populations at high risk of HIV perceiving themselves to be at low risk, as summarized in Table 4. This is illustrated by data from a study of 5606 Philadelphia residents undergoing rapid HIV testing, where the investigators categorized 71.6% of men and 60.0% of women as moderate/high risk; in contrast, only 56.8% of men and 8.3% of women perceived themselves to be high/moderate risk [34]. Populations reported to have low perceived risk include some MSM, despite their disproportionate HIV risk [8], and women at increased risk of HIV acquisition including Black women, women experiencing gender-based violence, and women involved in the criminal justice system [8, 35–37]. One study also highlighted “lack of concern about HIV” as a barrier to PrEP uptake in adolescent and young adult transgender men and women [38].

Another related individual-level barrier to PrEP access is low prioritization, which may be multifactorial. Prioritization may be a consequence of low HIV risk perception [39], substance use [40], or other behavioral health concerns [41]. In the USA, HIV prevalence is higher among people with serious behavioral health challenges (e.g., recurrent major depressive disorder, bipolar disorder, psychotic disorder, or comorbid mood disorder) compared with the general population [41–43]. Social factors related to poverty that limit women’s access to antiretroviral therapy [44] may also impact PrEP prioritization: a 2017 review noted that “unemployment, unstable housing, and food insecurity may render accessing PrEP and taking PrEP as unimportant if women are unable to fulfill their basic needs for food and shelter” [45]. Another setting in which accessing PrEP may be deprioritized is for MSM who are released from incarceration: one study participant stated, “When you go home you have so much to do... you have to go back to welfare to get food stamps... so much different stuff... you’re not really going to be thinking about ‘I’ve got to go to the doctor’s [office] right away to get my PrEP’” [46]. Competing priorities have also been identified as major barriers to healthcare in general among homeless adults,

for whom meeting basic needs for food, shelter, and safety outweigh healthcare needs [47].

PrEP implementation may also be reduced as a result of insufficient ascertainment of HIV risk by healthcare providers. In a survey of advanced practice nurses in Indiana, their comfort with discussing/prescribing PrEP was about 80% with gay or heterosexual couples in a monogamous relationship with one partner living with HIV infection, about 70% for PWID, and 60% for MSM who did not indicate their relationship status [48]. In a survey of health directors in North Carolina ($N = 56$), a perceived lack of suitable PrEP candidates was reported by 26% of respondents from departments not prescribing or referring individuals for PrEP [23]. Recently, a paradox concerning perception of risk and willingness to prescribe has been noted in an online survey completed by 111 medical students [49]. Results showed that willingness to prescribe was inconsistent with patient risk, with fewer students willing to prescribe PrEP if the patient was engaging in riskier behaviors such as not using condoms or having multiple partners. This was attributed to misconceptions about the effectiveness of PrEP and to personal biases related to sexuality and sexual orientation.

SOCIAL STIGMA AS A BARRIER TO PREP UPTAKE

Social stigma perceived and/or experienced by individuals at risk of HIV is a major barrier to PrEP use (Table 5). This may stem from historical stigma surrounding HIV/AIDS (both the disease itself and being a member of a group considered at risk, i.e., sexual, gender, racial and/or ethnic minority); for example, transgender women in one focus group had concerns that by taking PrEP they would be mistakenly identified as HIV-positive [50]. It may also be stigma relating specifically to PrEP. The latter is largely attributable to “PrEP shaming”—the belief that PrEP users engage in reckless sexual behavior—and was a topic of much debate following the labeling of PrEP users as “Truvada whores” in 2012 [51, 52]. The evidence summarized in Table 5 suggests that PrEP stigma

persists: participants from several studies reported experience of PrEP-related stigma that manifested in a number of ways, including stereotyping, rejection, and discrimination (including homophobia, transphobia, racism, and sexism), all of which were identified as barriers to PrEP use (Table 5).

The social stigma experienced by individuals may be compounded by PrEP-related stigma at the healthcare provider level. Some providers have been concerned by an increase in sexual behavior by PrEP users due to their perception that their HIV susceptibility is decreased, known as “risk compensation,” and this may foster reluctance to prescribe PrEP [53–56]. A survey of 266 primary care physicians found those who had never prescribed PrEP or referred one of their patients for PrEP were more likely to believe that PrEP use would lead to risk compensation compared with those who had adopted PrEP (prescribed/referred) [53]. In a survey of 573 providers in the USA and Canada, risk compensation was also identified as a reason for providers not prescribing PrEP. Respondents were concerned that PrEP could create a “false sense of security,” and that if individuals would not use condoms then they would not use pills. Assumptions made by providers impact their perception of the likelihood of risk compensation. One study found medical students to stereotype Black MSM as more likely than White MSM to engage in increased condomless sex when on PrEP. This racial bias was associated with reduced willingness to prescribe PrEP [57].

PROVIDER BIAS AND DISTRUST OF HEALTHCARE PROVIDERS/SYSTEMS AS A BARRIER TO PREP UPTAKE

Implicit racial and ethnic bias by healthcare professionals in the USA is well documented and can impact treatment decisions. One systematic review identified 15 studies that assessed implicit bias by healthcare professionals; 14 of these studies reported low-to-moderate levels of racial/ethnic bias among healthcare

professionals. This implicit bias was significantly related to treatment decisions, patient–provider interactions, adherence, and, critically, patient outcomes [58]. A second systematic review found that 31/37 eligible studies reported racial/ethnic bias among US healthcare professionals, and of 14 studies that related bias with outcomes, six related higher implicit bias with treatment disparities [59]. Further, according to the 2011 “Report of the National Transgender Discrimination Survey” of 6540 transgender and gender non-conforming people across all 50 states, one-fifth reported being refused care, and almost one-third had been subject to harassment in a healthcare setting [60]. Beyond the individual provider level, there are also systemic biases: a widely used algorithm in US healthcare systems was found to exhibit significant racial disparity [61]. For patients assigned the same risk level by the algorithm, in reality, Black patients had increased signs that their medical condition was not controlled, compared with White patients with the same condition. This bias arose because the algorithm made predictions based on cost, rather than illness, which reflected spending inequalities for Black and White patient communities. It is unsurprising, therefore, that there remains a significant level of distrust of healthcare systems among some patient groups.

Distrust of healthcare providers/systems was identified as a key barrier to PrEP uptake (Table 6), particularly in populations with disproportionate HIV risk. As noted previously, feelings of distrust may be attributed to social stigma at the provider level; in a number of studies, participants were alienated from their healthcare system as a result of experienced and anticipated discriminatory judgment from providers in the form of racism or homophobia (Table 6). Furthermore, there have been a number of malign events in the US medical establishment that have led to distrust in the healthcare system, particularly for Black communities (e.g., the Tuskegee syphilis study, the case of Henrietta Lacks, and the 1946–1948 Guatemalan sexually transmitted disease experiments) [62–65]. Medical distrust can also manifest as conspiracy beliefs; such beliefs have acted as a barrier to HIV prevention in the USA

for years, with high prevalence within some Black communities attributed to historical racial discrimination [66–68]. A similar pattern seems to be emerging with respect to PrEP. In a survey of Black and White MSM and transgender women who have sex with men ($N = 264$), conspiracy beliefs related to PrEP were endorsed by 42% of the population and were more frequently reported by Black than White participants. These beliefs included “The CDC cannot be trusted to tell gay communities the truth about PrEP” and “When it comes to PrEP, drug companies are lying and taking advantage of us” [68]. Other studies support high prevalence of HIV conspiracy beliefs among Black MSM in the USA, one of which reported a lower intention to adopt PrEP among those with a conspiracy belief [69, 70].

Finally, some patients may also have doubts about the validity of clinical data for the use of PrEP in specific patient groups. Black MSM, cisgender women, and transgender women have been reluctant to participate in clinical research, and consequently are underrepresented in clinical trials [71–73]. One study found that lack of data on PrEP in specific populations was a barrier to PrEP uptake [50].

LACK OF ACCESS TO MEDICAL CARE AS A BARRIER TO PREP UPTAKE

At the individual level, there are simple logistical constraints to accessing PrEP, exacerbated by socioeconomic inequalities. For example, individuals may experience difficulty in getting to the clinic [74] due to lack of transportation [46] or time constraints [75, 76]. A 2016 National Survey on HIV in the Black community found that 38% of 787 participants were more than one hour’s drive from a PrEP provider. People living in regions with higher PrEP clinic density were found to be significantly more willing to use PrEP [77]. Individuals at risk may also lack access to providers where PrEP is routinely offered [78], or may not have access to medical care of adequate quality, such as lesbian, gay, bisexual, transgender, and queer (LGBTQ)-sensitive care [79].

PrEP access by individuals at risk may also be impeded by barriers at the healthcare system/provider level [80]. Many of these are logistical barriers present in the healthcare system, such as pharmacy impediments (e.g., difficulty having prescriptions filled) [20, 81], lack of formal prescribing protocols [82], or absence of service provision in certain geographic locations [23, 82, 83]. For example, in a county-level analysis, the Southern region of the USA was found to account for only one-quarter of PrEP-providing clinics, despite representing over half of all new HIV diagnoses. Of note, the disparity in PrEP clinic density in Southern USA also contradicts need in terms of underrepresentation in areas with lower income, higher Black and Latinx/Hispanic populations, and less insurance coverage [82]. Another barrier to PrEP access at the healthcare system level is limited delivery of PrEP to difficult-to-reach populations, such as PWID and homeless individuals, on account of inadequate infrastructure, which will need to be addressed through innovative strategies [83, 84].

FINANCIAL BARRIERS TO PREP UPTAKE

Financial concerns have been identified as common barriers to PrEP use across most populations at risk, including MSM, PWID, cisgender women, transgender women, young people, and homeless people (Table 7).

In addition to the studies highlighted in Table 7, media reports of insurance companies denying coverage to HIV-negative individuals who use PrEP [85, 86] and employers excluding PrEP from their insurance policies [87] have highlighted further barriers to accessing PrEP.

Patient concerns over insurance and ability to pay may in turn impact healthcare provider willingness to prescribe or discuss PrEP. For example, in one study of Washington State medical providers, while concerns about PrEP cost were frequent (43%), providers felt very (27%) or somewhat (45%) uncomfortable discussing cost and insurance issues [27]. In another study, low cost/insurance coverage was a facilitating factor for PrEP prescription by

physicians providing primary care to adolescents (13–21 years old) [31]. Furthermore, cost may be a factor in negative provider attitudes toward PrEP, with some dismissing the preventive therapy as an “expensive condom” [55].

A cost-related barrier to uptake of PrEP may also be lack of knowledge around co-pays, or the availability of financial assistance, i.e., how to find programs and, once found, how to navigate the program requirements [88]. Thus, patient concerns around cost are both a reflection of misinformation in general communities, as well as lack of knowledge and misinformation from the providers themselves.

SIDE EFFECTS/MEDICATION INTERACTION CONCERNS AS A BARRIER TO PREP UPTAKE

Another barrier to PrEP use is the experience and/or anticipation of PrEP side effects and/or medication interactions. Many studies, in various demographic populations, have captured concerns around short- and long-term safety of PrEP among individuals at risk (Table 8). Safety concerns were also reported in a large study at a New York City health center focusing on sexual and general health for LGBTQ communities; of 1208 PrEP users, 783 reported barriers; 67 reported side effects as a barrier to PrEP use, nine of whom stopped taking PrEP [20]. In addition, transgender individuals have specific concerns regarding PrEP and interactions with hormonal treatment [50, 89–91]. Finally, although there are no data in the literature to quantify the actual impact on PrEP uptake, anecdotally there are concerns that misleading lawyer advertisements about lawsuits concerning F/TDF in the USA may play into patients' concerns around PrEP side effects, leading them to discontinue or refuse PrEP medication [92]. Similarly, discussion of side effects on social media platforms could influence perceptions about PrEP and limit uptake [93–95].

Provider concerns around PrEP side effects and safety may impact their prescribing practices, exacerbating barriers to PrEP use. This barrier is closely linked with knowledge about PrEP and understanding of the benefit/risk

profile. A number of studies identified provider-level stigma with respect to PrEP safety; concerns around side effects/adverse events have been linked with negative attitudes toward PrEP and reduced intention to prescribe it [53, 55, 96, 97]. This is supported by a study of attitudes toward PrEP among physicians providing primary care to adolescents. Among 38 physicians who were interviewed, only 37% reported being somewhat or very familiar with PrEP, and concerns around side effects were identified as a barrier to PrEP use [31]. Similar findings were reported in a survey of internal medicine residents ($N = 48$), of whom 22% were unaware of PrEP and 62% had fair or poor awareness of side effects. PrEP was considered effective or safe by only 78% or 66% of participants, respectively [98].

BARRIERS TO PREP PERSISTENCE

Importantly, several of the key barriers to PrEP uptake discussed here have also been reported to hinder continued PrEP use (persistence). A study of 7148 individuals who initiated PrEP at a national chain pharmacy in the USA reported only 56% persistence in year 1, 63% in year 2, and 41% from initiation to year 2, with the lowest persistence in women and individuals aged 18–24 years. Factors predicted to contribute to PrEP cessation included financial barriers, changes in perceived risk, and difficulties accessing health-care services [99]. Overcoming barriers to PrEP uptake may therefore have a concurrent positive impact on adherence to PrEP.

POTENTIAL SOLUTIONS TO BARRIERS

Clinical trials and data demonstrating recent decreases in the frequency of new HIV diagnoses in areas of the USA where PrEP uptake has been greatest support the effectiveness of PrEP as an HIV preventive strategy [2–4, 100, 101]. In this review, key barriers to PrEP uptake were identified, including knowledge/awareness of PrEP; perception of HIV risk; social stigma; provider bias and distrust of healthcare

providers/systems; lack of access to medical care; lack of access to (or awareness of) financial assistance options; and PrEP side effects and medication interaction concerns (Table 1). The barriers described have tended to be observed in populations at greatest risk with the lowest PrEP uptake, and may also originate at the provider level. Furthermore, barriers that prevent uptake are not universal, and can be population-specific, exacerbated by co-prevalent syndemic conditions such as racism, homophobia, poverty, inadequate education, and behavioral health issues. The findings presented here have also been identified by others, who have noted similar common barriers overall [102–104] and in population groups at highest risk [105–112].

Improved education or training of individuals at risk and providers will be essential in overcoming a range of barriers to PrEP uptake. To raise awareness and uptake of PrEP among individuals at risk, delivery of brief educational sessions for visitors to sexual health clinics could be an effective approach [113], as could provision of online resources such as those developed by the New York City Department of Health and Mental Hygiene [114] and The National Lesbian, Gay, Bisexual and Transgender (LGBT) Health Education Center at the Fenway Institute [115]. Social marketing campaigns also have the potential to reach millions of individuals, as demonstrated by the PrEP4Love campaign in Chicago [116]. However, despite the well-documented need to increase awareness of PrEP, a recent systematic review found that very few ongoing studies were addressing this need, particular noting a paucity of research on educational interventions targeted at cisgender women, transgender women, transgender men, PWID, and in Southern regions of the USA [117].

Education may also instill trust in healthcare providers/systems among individuals at risk. For example, improved accessibility and credibility of HIV prevention messaging in minority sub-populations has been proposed as a strategy to negate the impact of PrEP-related conspiracy beliefs [70]. Social media-based, peer-led interventions could also confer a significant population-level impact on PrEP uptake among young Black and Latinx individuals by addressing issues such as knowledge/awareness,

Table 5 Summary of recent data indicating that social stigma is a barrier to PrEP uptake among individuals at risk of HIV

Demographic variable	Study design	Summary of data	References
Sexual orientation	Interview of HIV-negative MSM who use PrEP ($N = 43$)	PrEP stigma was experienced as rejection by potential/actual partners, being subject to stereotypes of promiscuity/chemsex, and labeling (both the user and the medication)	[51]
	Interview of incarcerated MSM at the Rhode Island Department of Corrections ($N = 26$)	Post-release barriers to PrEP uptake and adherence included anticipated partner or family disapproval	[46]
	Interview of Black MSM PrEP users in Los Angeles ($N = 26$)	Participants reported multiple experiences of PrEP-related stigma, including the perception of elevated sexual risk behaviors; conflicts in relationships; assumptions that users are HIV-positive; and gay stigma in families	[174]
	Focus groups of MSM in New York City ($N = 24$)	Participants thought that stigma against PrEP users was declining as PrEP became more common, but stigma remained for those not using condoms and in relation to suspicions of infidelity with PrEP use	[175]
	Focus groups of young men and TGM and TGW who have sex with men in Boston, Chicago, and Los Angeles ($N = 36$)	Stigma and marginalization were highlighted as barriers to PrEP use	[176]
	Focus groups of gay, bisexual, and other MSM in Boston, Massachusetts and Jackson, Mississippi ($N = 35$)	Participants from Jackson, in particular, expressed fear that information would be disclosed to family and friends. One person suggested that stigma related to gay sex might be a barrier to people seeking PrEP	[167]
	Interview of MSM in the USA ($N = 3932$) and Sub-Saharan Africa ($N = 4063$)	Individuals in the USA were more likely to avoid healthcare support/intervention if they had not disclosed their sexual behavior to their family	[177]
	Interview of current and potential PrEP users in Alabama ($N = 44$), the majority of whom were gay or lesbian (66%) ^a	Sexuality-related stigma was raised as a perceived barrier to PrEP access	[76]
Gender	Focus groups of TGW living in New York City ($N = 18$)	Stigma and exclusion of TGW from advertising were identified as barriers to PrEP use	[50]
	Online survey of HIV-negative, heterosexually active PrEP-inexperienced women in Connecticut who were planning parenthood ($N = 597$)	PrEP-user stereotypes were commonly experienced, with many believing others would regard them as promiscuous (37%), HIV-positive (32%), bad (14%), or gay (11%). Thirty percent reported they would feel ashamed to disclose PrEP use; many expected disapproval from family (36%), sexual partners (34%), and friends (25%)	[178]
	Group discussions among cis and TGW of color at the “Empowering Women’s Health Summit” in 2018 ($N = 279$)	Participants identified cultural gender norms and roles as an overarching barrier to PrEP use; other barriers included lack of effective communication with healthcare providers, structural racism, and stigmatization	[179]
Race/ethnicity	Survey of HIV-negative cis women who completed enrollment for a PrEP clinical trial in Southern California ($N = 136$)	Black women were less likely to know if their partner was HIV-positive, compared with White and Latina women	[180]

Table 5 continued

Demographic variable	Study design	Summary of data	References
History of substance abuse	Interview of HIV-negative PWID in Boston and Providence ($N = 33$)	HIV-related stigma within social networks was identified as a barrier to PrEP use	[84]
	Survey of PWID recruited to a mobile syringe exchange program in New Jersey ($N = 138$)	Participants reported substantial barriers to PrEP, including feeling embarrassed (45%) or anxious (52%) about taking PrEP, and nondisclosure to partners (51%)	[78]
Age	Survey of young (age 18–30 years) HIV-positive minorities in South Texas ($N = 92$)	A total of 43% of participants reported that they would be embarrassed to ask for PrEP	[166]
	Survey and interview of young adults experiencing homelessness in Houston ($N = 30$) or Los Angeles ($N = 15$)	Identified barriers to PrEP use included perceived stigma of PrEP use	[165]
	Interview of physicians providing care to 13–21-year-old adolescents ($N = 38$)	Participants reported lack of acceptability to parents as a barrier to PrEP use	[31]
	Survey of young MSM in California using geosocial networking apps ($N = 687$)	Stigma was identified as a factor in low willingness to take PrEP, e.g., concern around family members or friends finding out about PrEP use	[181]
	Survey of PrEP-indicated emerging MSM aged 18–25 years ($N = 194$)	Only approx. 20% of participants reported moderate or high comfort with parent sex communication. Odds of current PrEP use increased with age, parent sex communication, and increased family disclosure of sexual identity. Participants who reported being in a relationship were less likely to be using PrEP than single participants	[182]
	Survey of MSM aged 18–25 years ($N = 236$)	Participants were less likely to use PrEP if they were in a relationship	[183]
	Online surveys and focus groups of adolescents ($N = 56$), most of whom were cis male (95%) and identified as gay (79%)	A frequently reported barrier was homophobia in the form of disapproving parents and healthcare providers	[74]
	Online focus groups of HIV-negative sexual and gender minority adolescents (aged 14–18 years) recruited from across the USA	Participants asked a variety of questions about PrEP, including how or where to get PrEP without parents finding out	[184]
Geographic location ^a	Focus groups of individuals at high risk of HIV in the Deep South ($N = 54$), primarily Black MSM and women participating in substance use treatment	Participants described substantial levels of stigma, including HIV-related stigma and discrimination from family, church, and community	[185]

cis cisgender, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *PrEP* pre-exposure prophylaxis, *PWID* people who inject drugs, *TGM* transgender men, *TGW* transgender women

^a Please see study of current and potential PrEP users in Alabama “Sexual orientation” category, also applicable here [76]

attitudes, stigma, and treatment access [118]; similar interventions could successfully reach transgender women and MSM. Counseling on the benefits of PrEP, and providing information and reassurance on the risk and monitoring of short- and long-term side effects, may also improve adherence to PrEP [119].

It is also imperative that educational interventions are targeted to primary care providers, including training to increase PrEP knowledge [120] and to alleviate concerns regarding PrEP safety [98]. Concerns around risk compensation (or an increase in risk-taking behaviors among individuals at risk prompted by a decrease in perceived HIV risk) appear to be one factor that can cause reluctance among some healthcare providers to prescribe PrEP to eligible patients [53]. While several studies have reported risk compensation behavior in individuals receiving PrEP [121–123], the balance of evidence suggests that patients who are eligible for PrEP inherently have a high baseline risk for STIs, which remains high following initiation of treatment with PrEP [88, 124–128]. Even if risk compensation does occur in some individuals or populations, related concerns do not justify withholding PrEP from people at risk for HIV infection [56]. Consistent with this notion, it has been proposed that PrEP be viewed as an opportunity for improved STI control [124, 129], whereby an increase in detection rates due to more frequent STI testing, with potentially earlier diagnosis and treatment, may counteract or surpass any negative effects of risk compensation [130]. Nevertheless, patients receiving PrEP should be provided with support for risk-reduction behaviors [33]. Similarly, misconceptions around the development of treatment resistance may also account for the reluctance of some providers to prescribe PrEP [24, 31]. However, there is little evidence supporting the development of treatment resistance with the use of PrEP medications. The number of reported cases is extremely low, with the majority occurring in individuals with undiagnosed HIV infection or during sporadic unsupervised use [32, 33, 131], thus highlighting the importance of testing for HIV prior to PrEP initiation and regularly during use of PrEP, per clinical guidelines [33].

Education targeted to primary care providers has been shown to be effective: after an educational intervention, the proportion of participants (internal medicine residents) who believed PrEP was safe increased from 66% to 92% and the proportion who believed it was effective increased from 78% to 94%. Before training, only one-third of participants were likely to prescribe PrEP in the next 6 months, which increased to two-thirds after training [98]. Healthcare professionals wishing to prescribe PrEP and who want to learn more about its implementation can refer to current CDC/US Public Health Service (USPHS) clinical guidelines for comprehensive information on the use of daily oral antiretroviral PrEP to reduce the risk of acquiring HIV infection in adults [33]. Complementary information can also be found in the World Health Organization implementation tool for PrEP of HIV infection [132] and the US Preventive Services Task Force Recommendation Statement on PrEP [133, 134]. A summary of guidance for implementing PrEP in clinical practice is provided in Table 9.

Training may also be employed to improve cultural humility [104] and to overcome the potential impact of implicit bias, stereotypes, and anticipated risk compensation on willingness to prescribe [135]. However, to truly address bias entrenched in the healthcare system, changes need to be made at a societal level. The ultimate aim should be that the healthcare community workforce adequately reflects the populations it treats; programs that increase the number of Black, Latinx, and LGBTQ healthcare professionals are needed.

Some individual-level barriers to access, such as not knowing where to get PrEP [74, 136], should be relatively straightforward to address through improved communication with individuals at risk. However, improving access to PrEP will require innovative approaches to delivery of care. It is important that these strategies extend PrEP outreach by engaging a diverse range of providers, including those from non-traditional settings such as pharmacies, mental health clinics, substance use clinics, emergency rooms (ERs), HIV testing centers, correctional institutions, and community-based organizations [137]. For example, integration of

HIV screening into ERs has been highly successful [138]. This and the apparent willingness of individuals who are at risk to accept PrEP from ER providers suggest that ERs could provide a setting to facilitate quick connections with PrEP providers [137]. For non-emergency settings, pharmacies should play an important role in PrEP implementation in the community [104]. The One-Step PrEP[®] program, a pharmacist-managed approach that allows PrEP access following a single patient encounter, has been shown to be logistically and financially feasible, with positive responses from individuals seeking PrEP [139, 140]. Between March 2015 and February 2018, 695 patients initiated PrEP via the One-Step PrEP[®] program and 98% had a zero-dollar patient responsibility per month. The dropout rate was 25%, and although 207 sexually transmissible infection diagnoses were made, no HIV seroconversions were reported [141]. State legislation, such as California Senate Bill 159, which allows pharmacists to provide PrEP medications without a prescription, may further expand pharmacist-led PrEP efforts and access in the USA. Integration of mental health screening into HIV healthcare has also been proposed as a strategy to improve HIV prevention [41]. Regardless of treatment setting, the development of stronger guidelines and policies for PrEP providers [97], along with the establishment of partnerships and effective communication between medical and social service providers [102], is needed. The World Health Organization reported that one of the critical enablers for programs to prevent and treat HIV was addressing basic needs, such as shelter, food, hygiene, childcare, recreation, and employment [142]. PrEP prevention programs targeted to certain populations may need to collaborate with programs and agencies who can provide this support.

Leveraging technology can make PrEP accessible to more patients; PrEP uptake may be supported by app-based delivery models such as TelePrEP, which connects individuals to a PrEP provider using a phone or computer [14, 143]. Similar approaches designed to reduce the patient and provider burden may also encourage PrEP persistence. As an illustration, the “PrEP@Home” model, designed to decrease

monitoring by replacing quarterly PrEP follow-up visits with home care, was found to be acceptable by participants in a pilot study, and was in demand for future use [144]. This approach could be especially valuable to those without access to transportation [144] or those affected by the stigma of HIV. A pharmacy-based TelePrEP model was implemented in a large county hospital in Atlanta in February 2018: 41 out of 44 patients who started PrEP (93%) remained on PrEP in 2019 [145].

Among the easily surmountable barriers to PrEP uptake may be treatment cost and insurance coverage. While there is evidence to support cost as a perceived barrier to PrEP uptake for those who present for PrEP, the actual scale of this problem may be limited. A recent independent study of nationally representative data, including authors from the CDC, demonstrated that fewer than 1% of the individuals with indications for PrEP required financial assistance for both PrEP medication and clinical care [146]. An additional 7% required financial assistance only for PrEP clinical care (not PrEP medication). Thus, only a small number of patients were not financially covered for clinician visits or laboratory tests, and an even smaller number had no coverage for medication and clinical costs of PrEP care [146]. Regardless, there is a proportion of patients, albeit small, with an unmet need for financial assistance in PrEP care. Efforts of the US Department of Health and Human Services’ “Ready, Set, PrEP” program may help to address the unmet need in this population through provision of PrEP medication at no cost to qualifying recipients. This initiative is a component of the US government’s wider plan to “End the Epidemic,” which aims to reduce new HIV infections in the USA by 75% in 5 years and by 90% by 2030 [147, 148].

Starting in 2021, on the basis of the Affordable Care Act, private insurers will be obliged to cover PrEP as a result of the intervention receiving Grade A recommendation from the US Preventive Services Task Force [133, 134]. In addition, 2019 saw the introduction of the PrEP Access and Coverage Act to the Senate, which would require all private and public insurance plans to cover the costs of accessing PrEP [149].

Table 6 Summary of recent data indicating that distrust of healthcare providers/systems is a barrier to PrEP uptake among individuals at risk of HIV

Demographic variable	Study design	Summary of data	References
Sexual orientation	Survey of MSM at two Atlanta-based Gay Pride events in 2018 (<i>N</i> = 381)	More than half of participants were willing to be screened for PrEP in pharmacy (with Black MSM being significantly less willing than White MSM) and one-third were unwilling to discuss PrEP with pharmacy staff	[186]
	Focus groups of MSM in New York City (<i>N</i> = 24)	Many participants reported mistrust of medical providers	[175]
	Interview of gay, bisexual, and other MSM involved in the criminal justice system (<i>N</i> = 26)	Participants noted the following reasons for mistrust: feelings of dehumanization; lack of privacy leading to belief that medical care is not confidential; and belief that status as an incarcerated person influences care received	[187]
	Survey of Black MSM in Southeastern USA (<i>N</i> = 147)	Perceived healthcare-related discrimination was negatively associated with PrEP awareness	[188]
	Focus groups of Black MSM aged 16–25 years in Milwaukee (<i>N</i> = 44)	Previous/anticipated negative interactions (perceived racism/homophobia) with physicians and skepticism about the healthcare system were reported to have alienated young Black MSM from the healthcare system and created barriers to PrEP use	[189]
	Interview of Black MSM PrEP users (<i>N</i> = 26)	Participants reported judgement from medical providers, and discomfort with medical providers	[174]
	Focus groups of gay, bisexual, and other MSM in Boston, Massachusetts and Jackson, Mississippi (<i>N</i> = 35)	Participants from Jackson had a palpable and emphatic degree of medical mistrust, and described a strong aversion to medical care in Black communities; they also expressed skepticism about the effectiveness of PrEP	[167]

Table 6 continued

Demographic variable	Study design	Summary of data	References
Gender	Data from HIV-negative TGW aged 16–29 years enrolled in Project LifeSkills during 2012–2015 ($N = 230$), the majority of whom were of color (67%)	Having a medical provider who meets health needs was associated with higher PrEP acceptability scores	[164]
	Group discussions among cis and TGW of color at the “Empowering Women’s Health Summit” in 2018 ($N = 279$)	Distrust of medical providers was identified as a barrier to PrEP use	[179]
	2017 cross-sectional survey of HIV-negative, PrEP-inexperienced and heterosexually active adult women ($N = 501$)	Black women expressed higher levels of medical mistrust than White women, which was also associated with lower comfort discussing PrEP	[190]
	Focus groups and interviews with TGW in San Francisco ($N = 30$)	Transgender-specific barriers included medical mistrust due to transphobia	[89]
Race/ethnicity	^{a,b,c}		
History of substance abuse	Interview of HIV-negative PWID in Boston and Providence ($N = 33$)	Negative experiences with healthcare providers was identified as a barrier to PrEP use	[84]
Age ^b	Cross-sectional data from an ongoing cohort study of young sexual-minority men in New York City ($N = 492$)	Participants with greater concerns around talking with their provider about their sexual behaviors were less likely to use PrEP	[191]
	Online surveys and focus groups of adolescents ($N = 56$), most of whom were cis male (95%) and identified as gay (79%)	A frequent barrier to PrEP use was homophobia in the form of disapproving healthcare providers	[74]
	Survey of young MSM in California using geosocial networking apps ($N = 687$)	Greater medical mistrust was associated with lower willingness to take PrEP	[181]

cis cisgender, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *PrEP* pre-exposure prophylaxis, *PWID* people who inject drugs, *TGW* transgender women

^a Please see study of Black MSM in the “Sexual orientation” category, also applicable here [188]

^b Please see study of Black MSM aged 16–25 years in the “Sexual orientation” category, also applicable here [189]

^c Please see study of Black MSM in the “Sexual orientation” category, also applicable here [174]

Despite this, addressing the financial barriers to PrEP will require affordable and high-quality insurance policies that are ubiquitously accessible to individuals at risk throughout the USA [104]. For example, dedicated PrEP service reimbursement programs have been introduced in several regions to financially assist

individuals at high risk of HIV acquisition, including those who are uninsured or underinsured [150–152]. A number of states now offer PrEP DAPs (Drug Assistance Programs), which pay for medical and laboratory costs incurred by PrEP DAP enrollees [153]. However, there is not yet much overlap between the states offering

Table 7 Summary of recent data indicating that financial concerns are a barrier to PrEP uptake among individuals at risk of HIV

Demographic variable	Study design	Summary of data	References
Sexual orientation	Qualitative phone interviews with attendees at a sexual health clinic in New York City (<i>N</i> = 1208)	58 of 1208 patients who initiated PrEP reported barriers stemming from insurance issues	[20]
	Patients with recently diagnosed HIV (<i>N</i> = 268, mainly MSM)	Cost/insurance concerns were reported as barriers in 36% of patients	[161]
	Interviews with MSM at Rhode Island Department of Corrections (<i>N</i> = 26)	Most participants were interested in taking PrEP, but were concerned that access to health insurance may be necessary to help with the cost	[46]
	A large survey of young MSM (<i>N</i> = 2297)	PrEP use was associated with having health insurance	[10]
	Mixed-methods study of 14–18-year old MSM (<i>N</i> = 56)	Paying for PrEP was frequently cited as a barrier	[74]
Gender	Interviews with women attendees at an urban sexual health clinic (<i>N</i> = 14)	Lack of insurance coverage was a concern	[81]
Race/ethnicity	Group discussions with cis and transgender women of color in South Florida (<i>N</i> = 279)	Insurance coverage and lack of economic independence were cited as barriers	[179]
Age	^a		
History of substance abuse	A survey of PWID in New Jersey (<i>N</i> = 138)	33% reported lack of insurance as a barrier to PrEP use	[78]
Geographic location	Strengths-based case management intervention in Florida (<i>N</i> = 30, mostly male, Hispanic, and Black)	Financial barriers to PrEP were encountered by 67% (20/30) of adults	[80]
Marginalized populations	Behavioral intervention trial in female sex workers in the Mexico–US border region (<i>N</i> = 295)	18.7% of individuals cited perceived financial barriers to PrEP	[192]
	Mixed methods study of young adults experiencing homelessness in Houston and Los Angeles (<i>N</i> = 45)	Cost was identified as a barrier to PrEP use	[165]

cis cisgender, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *PrEP* pre-exposure prophylaxis, *PWID* people who inject drugs

^a Please see study of 14–18-year-old MSM “Sexual orientation” category, also applicable here [74]

Table 8 Summary of recent data indicating that side effects/medication interaction concerns are a barrier to PrEP uptake among individuals at risk of HIV

Demographic variable	Study design	Summary of data	References
Sexual orientation	Focus groups of MSM in New York City ($N = 24$)	Concerns were raised about side effects of PrEP, and this was particularly the case among Black participants	[175]
	Focus groups of gay, bisexual, and other MSM in Boston, Massachusetts and Jackson, Mississippi ($N = 35$)	Participants concerns about side effects and safety	[167]
Gender	Survey of Black and Latina TGW in Baltimore and Washington ($N = 201$)	The most commonly reported barrier to PrEP uptake was worries about drug interactions with hormone therapy	[91]
	Focus group of TGW in New York City ($N = 18$)	Participants raised the barriers of uncomfortable side effects, difficulty taking pills, and lack of research in TGW	[50]
	Focus groups and interview of HIV-negative cis women visiting an STI clinic or emergency department in Chicago ($N = 370$), the majority of whom were Black (83%)	Most participants (81%) had concerns about taking PrEP, the most common being side effects (68%) and incomplete protection (25%)	[159]
	Interview of women experiencing intimate partner violence ($N = 26$)	Participants raised fear of side effects and long-term health concerns as potential barriers to PrEP	[35]
History of substance abuse	Interview of women at an urban sexual health clinic ($N = 14$)	Participants raised concerns about PrEP safety as a key barrier	[81]
	Interviews with TGW ($N = 60$) and TGM ($N = 90$)	About half were extremely or somewhat worried about the possibility of negative medical side effects of PrEP and 23% did not want to add another medication to their health regimen	[38]
	Interview of HIV-negative PWID in Boston and Providence ($N = 33$)	Participants raised concerns about PrEP side effects	[84]
Age	Survey of young MSM in California using geosocial networking apps ($N = 687$)	Concern about side effects was associated with reduced willingness to take PrEP	[181]

cis cisgender, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *PrEP* pre-exposure prophylaxis, *PWID* people who inject drugs, *STI* sexually transmitted infection, *TGM* transgender men, *TGW* transgender women

Table 9 Summary of PrEP implementation considerations based on the US Preventive Services Task Force Recommendation Statement [133, 134]**Identify individuals at risk**

Routinely assess sexual and injection drug use history for all patients in an open and nonjudgmental manner

Identify behaviors that make a person an appropriate candidate for PrEP

Complete baseline assessments in PrEP candidates

HIV testing and medical history to exclude persons with acute or chronic HIV infection

Kidney function testing

Serologic testing for hepatitis B

Serologic testing for hepatitis C

Testing for other STIs

Pregnancy testing (if applicable)

Consider vaccination for hepatitis A and hepatitis B in unvaccinated individuals

Patient counseling

Counseling points should include

The importance of adherence and its correlation to effectiveness

That PrEP does not reduce the risk of other STIs

Use condoms consistently to prevent other STIs

The importance of regular screening of STIs and the need to test once patient notices signs and symptoms of STIs

On-going follow-up and monitoring

HIV testing every 3 months

Regular screening for STIs

Continue to assess HIV risk

Other considerations

Identifying persons at risk of HIV can be challenging because of stigma and discrimination against gay, bisexual, transgender, and nonbinary persons, or the lack of a trusting relationship between patient and clinician

Recognize that adherence support is a key component of providing PrEP and includes establishing trust and open communication with patients, patient education, reminder systems for taking medication, and attention to medication adverse effects

Recognize the barriers to PrEP implementation and uptake; these barriers and disparities need to be addressed to achieve the full benefit of PrEP

Patients may discontinue PrEP for several reasons, including personal preference, decreased risk of HIV acquisition, or adverse medication effects

Consult the CDC guidelines for a complete discussion of implementations considerations for PrEP [33]

CDC Centers for Disease Control, *HIV* human immunodeficiency virus, *PrEP* pre-exposure prophylaxis, *STI* sexually transmitted infection

PrEP DAPs and states with the highest need (states without Medicaid expansion). Efforts are required to ensure patients are better informed about the financial assistance options available to them. To this end, patients require services to help them navigate sources of support, identify financial help [80, 154], improve access to treatment, and encourage positive engagement [80].

CONCLUSIONS

In summary, successful integration of PrEP into HIV screening and prevention services has the potential to reduce HIV incidence in the USA, and help achieve the US government's goal of ending the HIV epidemic in the USA by 2030 [147, 148]. However, optimal impact of PrEP as a preventive intervention is yet to be realized. This review has identified a complex and diverse range of barriers to PrEP uptake that exist at the social, structural, individual, and medical system/provider levels (Table 1). These include a lack of awareness of PrEP among eligible individuals and healthcare providers, fear of stigma and/or side effects, provider implicit bias, distrust of the healthcare system, and a lack of access to medical care or financial assistance. Among healthcare providers, misconceptions around the development of treatment resistance and/or the potential for risk compensation in PrEP users appear to be important factors behind the reluctance to prescribe PrEP. Overcoming these barriers will require multifaceted approaches that combine financial, social, structural, and educational interventions—not only addressing the practicalities of accessing PrEP but also acknowledging and addressing deep-rooted issues such as sociohistorical racism and systemic bias, combined with destigmatization of PrEP and its users (Table 1). Healthcare professionals wishing to prescribe PrEP can refer to current CDC/USPHS guidelines, the WHO clinical implementation tool, and the US Preventive Services Task Force Recommendation Statement (Table 9) [33, 132–134]. Furthermore, given that help for patients with navigating financial aid was identified as a barrier to uptake, both clinicians and patients

should be made aware of the “Ready, Set, PrEP” program, which offers access to PrEP medication at no cost for qualifying recipients in the USA. Finally, learnings from PrEP uptake may provide important insights for the implementation of any HIV prevention strategies that are yet to come.

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