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ORIGINAL PAPER

PrEP Uptake and Methamphetamine Use Patterns in a 4-Year U.S. National Prospective Cohort Study of Sexual and Gender Minority People, 2017–2022

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Abstract

Methamphetamine use is on the rise among sexual and gender minority people who have sex with men (SGMSM), escalating their HIV risk. Despite pre-exposure prophylaxis (PrEP) being an effective biomedical HIV prevention tool, its uptake in relation to methamphetamine use patterns in SGMSM has not been studied. In a U.S. cohort study from 2017 to 2022, 6,253 HIV-negative SGMSM indicated for but not using PrEP were followed for four years. Methamphetamine use was categorized (i.e., newly initiated, persistently used, never used, used but quit), and PrEP uptake assessed using generalized estimating equation (GEE), adjusted for attrition. Participants had a median age of 29, with 51.9% White, 11.1% Black, 24.5% Latinx, and 12.5% other races/ethnicities. Over the four years, PrEP use increased from 16.3 to 27.2%. GEE models identified risk factors including housing instability and food insecurity. In contrast, older age, health insurance, clinical indications, and prior PrEP use increased uptake. Notably, Latinx participants were more likely to use PrEP than Whites. Regarding methamphetamine use, those who newly initiated it were more likely to use PrEP compared to non-users. However, those who quit methamphetamine and those who persistently used it had PrEP usage rates comparable to those of non-users. Though PrEP uptake increased, it remained low in SGMSM. Methamphetamine use was associated with PrEP uptake. Healthcare providers should assess methamphetamine use for harm reduction. Prioritizing younger, uninsured SGMSM and addressing basic needs can enhance PrEP uptake and reduce HIV vulnerabilities.

Keywords PrEP uptake · Methamphetamine use patterns · Sexual and gender minority people who have sex with men (SGMSM) · U.S. national cohort study · Generalized estimating equation (GEE)

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Introduction

Among the estimated 1.2 million people living with HIV in the U.S., sexual and gender minority (SGM) people who have sex with men (SGMSM) are disproportionately affected [1]. Sexual minority men (SMM), including gay, bisexual, and other men who have sex with men, comprise 2–5% of the population yet they accounted for 70% of new HIV diagnoses in the U.S. in 2020 [2]. Pre-exposure prophylaxis (PrEP) is a highly effective biomedical tool for HIV prevention, reducing the risk of acquiring HIV by approximately 99% when taken as prescribed [3]. Despite its effectiveness, overall PrEP uptake is low, with less than one-third of individuals who could benefit from PrEP using it in the U.S [4]. Increasing access to and uptake of PrEP among populations vulnerable to HIV, including SGMSM individuals, is crucial to the success of the HIV prevention care continuum, without which all other steps are not feasible.

Methamphetamine has been an enduring and resurgent epidemic within SGMSM communities [5], with high rates of use among SGMSM populations ranging from 7.4 to 30% [6, 7]. The use of methamphetamine is strongly linked to factors that increase HIV risk, including enhancing libido and reducing inhibitions, which, when used for sexual enhancement, can lead to extended sexual encounters involving multiple partners [8–10]. In a previous study, we found that persistent methamphetamine users accounted for one-third of new HIV infections among our U.S. national cohort of SGMSM individuals [11].

In response to the U.S. methamphetamine epidemic and its impact on HIV infections in SGMSM populations, large-scale longitudinal studies are needed to understand its relations with PrEP use. Such information is crucial for developing targeted interventions and maximizing the effectiveness of PrEP as an HIV prevention strategy [12]. A recent systematic review has shown that SGMSM individuals who use substances are as likely as or more likely than non-substance using SGMSM to use PrEP, but they face challenges with adherence and persistence [13]. However, to our knowledge, no studies have examined the patterns of methamphetamine use and PrEP uptake among SGMSM populations, despite the significant role of methamphetamine in driving HIV infections and the importance of PrEP as a pillar of HIV prevention efforts. Longitudinal cohort studies allow for repeated assessments with temporal accuracy and offer a robust methodology for examining behaviors that occur naturally within real-world settings, to capture changes and changing associations over time [14].

In the current study, we report on PrEP uptake patterns and associated methamphetamine use in a U.S. national cohort of 6,253 SGMSM who were not taking PrEP at enrollment. Participants were assessed annually over four years. Understanding the patterns and determinants of PrEP uptake among SGMSM is integral to reducing HIV incidence in this highly vulnerable population. We specifically examine the association between methamphetamine use patterns and PrEP use. We hypothesized that, compared to non-users, (1) SGMSM who newly initiate methamphetamine would be more likely to use PrEP, (2) those who cease it would be less likely to use PrEP, and (3) persistent users would be more likely to use PrEP. Our goal is to inform PrEP care and refine PrEP strategies, targeting high priority populations to help end the HIV epidemic.

Methods

Study Population and Procedures

Data are from a cohort study, *Together 5,000* (T5K), which follows a U.S. national sample of cisgender men and transgender people who have sex with men. T5K is a longitudinal study designed to investigate missed opportunities for HIV prevention and PrEP uptake among populations with high vulnerability for HIV. Participants were recruited to complete baseline visits via advertisements on men-for-men geosocial networking applications between October 2017 and June 2018. Study inclusion criteria were cisgender men or transgender people aged 16 to 49 who, at the time of recruitment, had at least 2 male sex partners in the prior 3 months, were not currently participating in an HIV vaccine or PrEP clinical trial, not on PrEP at enrollment, reported living in the U.S. or its territories, reported that they were HIV-negative or did not know their HIV status, and met at least one of seven other factors associated with clinical indication for PrEP [15]. These factors are: engaging in receptive condomless anal sex acts with a male partner at least once in the past 3 months; engaging in insertive condomless anal sex acts with a male partner at least twice in the last 3 months; using methamphetamines in the past 3 months; being diagnosed with rectal gonorrhea or chlamydia in the past 12 months; receiving a syphilis diagnosis in the past 12 months; using post-exposure prophylaxis in the past 12 months; and sharing injection drug needles in the past 12 months. Additional details on enrollment procedures and study design have been published elsewhere [15, 16].

In total, 6,253 participants completed a baseline survey; 5,455 (87.2%) completed a 12-month assessment; 5,145 (82.3%) completed a 24-month assessment; 4,769 (76.3%) completed a 36-month assessment; and 4,264 (68.2%) completed a 48-month assessment. All participants in this analysis were cohort members eligible for PrEP (our main outcome) during the study, meaning they were HIV-negative. We excluded 194 individuals with HIV identified at

baseline and those who seroconverted during the study. It is possible that participants who seroconverted had used PrEP before. However, among the 303 participants who seroconverted, only 2 had used PrEP prior to seroconversion and they would not have made any meaningful impact on the analyses. Notably, no participants were taking PrEP at enrollment, despite being clinically indicated for PrEP, per inclusion criteria.

PrEP Uptake and HIV Testing

PrEP uptake was assessed through participants' self-reported current PrEP use during their annual assessments. This variable was time-dependent, with binary responses (yes/no) collected at 12-, 24-, 36-, and 48-month visits. To improve the accuracy of reported PrEP use, we asked participants who indicated taking PrEP to provide a digital photograph of their current (determined by date) PrEP prescription bottle for a $25 incentive. For individuals not currently using PrEP, we offered an equal $25 incentive for using an at-home OraSure HIV-1 specimen collection device (self-collected oral fluid HIV sampling kit) and mailing it in a pre-paid envelope to a laboratory for analysis [15]. Participants who reported having tested HIV-positive between study assessments (i.e., outside of the study) were asked to provide proof of diagnosis for a $25 incentive.

Predictors of PrEP Uptake

We examined factors associated with PrEP uptake, including demographic, socio-economic, and behavioral characteristics. Demographic variables included age and race/ethnicity; socio-economic variables included food insecurity, housing instability, and health insurance; and behavioral characteristics included patterns of methamphetamine use, clinical indication for PrEP, and a history of PrEP use. All variables, except race/ethnicity and history of PrEP use prior to enrollment, were time variant.

Race/ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Hispanic/Latinx, and all other races/ethnicities. We developed our measure of clinical indication for PrEP based on the Centers for Disease Control and Prevention's (CDC) 2017 clinical guidelines [17]. We defined clinical indication for PrEP in our study as having HIV-positive sexual partners in the past 3 months, engaging in any form of condomless anal intercourse (receptive or insertive) in the past 3 months, having condomless sex with cisgender women or HIV-positive cisgender men in the past 3 months, and receiving a diagnosis of bacterial sexually transmitted infections (STIs) such as syphilis, gonorrhea, or chlamydia in the past 6 months. Individuals who injected drugs and shared injection equipment were also indicated for PrEP. Health insurance was assessed by asking participants whether they had coverage at the time of the annual assessments (yes/no). Food insecurity was measured using the U.S. Department of Agriculture's Household Food Security Survey Module, a standardized, six-item scale with 3 categories (food secure, low food security, very low food security) [18]. For our analysis, we combined low and very low food security into a single category of food insecurity. Sample items included, "In the last 12 months, did you ever eat less than you felt you should because there wasn't enough money for food?" with response options of yes, no, and don't know. Housing instability was determined by asking participants whether they had experienced periods of unstable housing in the past year, such as living in a car or a shelter, couch surfing, or being homeless. These two variables were selected as proxies for socio-economic status, as they captured ongoing struggles related to meeting basic needs more directly than variables such as income or education.

Considering the heightened risk of HIV associated with methamphetamine use, we included history of methamphetamine use in our analysis. To capture its complex relation with PrEP use and control for the effect of longitudinal confounding, we created a variable that captured methamphetamine use over the prior two years. At each time point, we asked participants if they had used methamphetamine for non-medical purposes in the previous year (yes/no). We combined prior year methamphetamine use and its one-time-lagged measurement into four groups: no methamphetamine use (no methamphetamine use in the past two years), quit methamphetamine (used methamphetamine in the year before last but not the past year), initiated methamphetamine (did not use methamphetamine in the year before last but used it in the past year), and persistent methamphetamine use (methamphetamine in both of the past two years). Participants reporting prior PrEP use before baseline were categorized as having a history of PrEP use (note that all participants reported no current PrEP use at enrollment given that it was a study inclusion criteria).

Statistical Analysis

To describe the baseline characteristics of T5K, we used frequencies and percentages for categorical variables and median and interquartile range (IQR) for age (a non-normally distributed continuous variable). We reported annual rates of PrEP uptake through 2022.

To explore both time-varying and time invariant factors associated with PrEP uptake, we conducted bivariate and multivariable analyses using generalized estimating equation (GEE) models with a logit link function. GEE models are marginal models well-suited for longitudinal data with

Table 1 Baseline characteristics of sexual and gender minority individuals in a U.S.-based longitudinal cohort, *Together 5,000*, 2017–2022

Characteristic	*n (%)* or median (IQR)
Total	6253 (100%)
Age	29.0 (25.0–36.0)
Race/ethnicity	
Non-Hispanic White	3247 (51.9%)
Non-Hispanic Black	691 (11.1%)
Hispanic/Latinx	1531 (24.5%)
Other	784 (12.5%)
Food insecurity	
No	3134 (50.1%)
Yes	1737 (27.8%)
Missing	1382 (22.1%)
Had unstable housing	1910 (30.5%)
Clinically indicated for PrEP	6253 (100%)
Had health insurance	4535 (72.5%)
Had PrEP use history	895 (14.3%)
Used methamphetamine in the past	1447 (23.1%)

Note Since we did not ask questions on food security at baseline, we used food security at 12 months as the baseline. The constructed variable "methamphetamine use in the past two years" is not available at baseline. Instead, we used "methamphetamine use in the past" at enrollment

repeated measures [19]. We modeled age using restricted cubic splines with three even knots at its quartiles to allow for a non-linear relationship, avoiding categorization into age groups that may result in loss of information. Cubic splines are commonly used for spline modeling and 3–5 knots are recommended to be sufficient [20]. This approach is more parsimonious and informative compared to using indicator variables for each age group. To account for longitudinal attrition and missingness bias, we employed inverse probability of censoring weighting (IPCW) in the multivariable analysis [21, 22]. Our previous research has suggested that certain baseline characteristics (i.e., age, gender, race, employment status, education, income, health insurance status, housing instability, sexual orientation, and sex worker status) were associated with completing all baseline study measures [23]. Thus, we created inverse probability weights using logistic regression to estimate the probability of completing each assessment for all enrolled participants, and extreme weights (> 95%) were trimmed by replacing trimmed weights with the 95th percentile weight value.

In the final, observation-weighted multivariable GEE logistic regression model, we included time points, age, race/ethnicity, housing instability, clinical indication for PrEP, health insurance, history of PrEP use (at baseline), and methamphetamine use in the past two years based on prior research, literature, and modeling. We reported odds ratios (OR) and 95% confidence intervals (CIs) for all variables. As there were time-dependent covariates within the same cluster, we used independence working correlation to obtain within-population average associations [24, 25]. We compared the results from the weighted multivariable model with those from the unweighted model to assess estimate robustness. We created a weighted multivariable model to obtain odds ratio of age as a categorical variable (i.e., 15–24, 25–34, 35–44, 45–54 years), which was not available in spline modeling, controlling for the same covariates as the other multivariable model. Statistical significance was determined at a p-value ≤ 0.05. Statistical analyses were performed using the geeglm function of the geepack package in R 4.2.2. (R Core Team, Vienna, Austria).

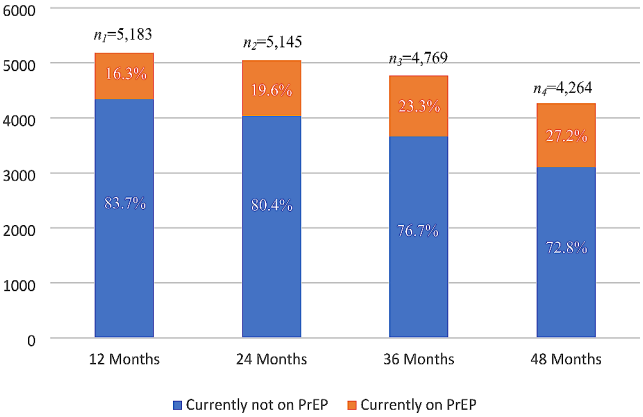

Fig. 1 PrEP use vs. non-use among sexual and gender minority people over 48 months, *Together 5,000*, 2017–2022

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of our study sample, consisting of 6,253 participants who were clinically indicated for PrEP but not taking PrEP at enrollment. The median age at baseline was 29.0 (IQR: 25.0–36.0) years, with 51.9% being White, 11.1% Black/African American, 24.5% Hispanic/Latinx, and 12.5% belonging to other races/ethnicities. Most participants reported having health insurance (72.5%). 23% (23.1%) of participants reported past methamphetamine use and 27.8% and 30.5% experienced food insecurity and housing instability in the past year, respectively. 14% (14.3%) of participants reported a history of PrEP use prior to enrollment.

Rates of PrEP Uptake

In total, during the 4-year follow-up, 2,321 out of 6,253 participants (37.1%) started taking PrEP. Figure 1 displays the rates of PrEP use over time. At 12 months, 843 out of 5,183 participants (16.3%) initiated PrEP. At 24, 36, and 48 months, 1,007 out of 5,145 (19.6%), 1,110 out of 4,769

(23.3%), and 1,160 out of 4,264 (27.2%) participants were taking PrEP, respectively.

Bivariate Results of GEE Models

Table 2 reports the results of bivariate GEE models of characteristics associated with PrEP uptake over four years. Among participants who were clinically indicated for PrEP but not using PrEP at enrollment, factors associated with PrEP uptake during the study included older age, being clinically indicated for PrEP at the time of the annual assessment (OR: 2.63, 95% CI 2.32–2.98, P < 0.001), having health insurance (2.40, 2.10–2.75, P < 0.001), and a history of PrEP use (2.05, 1.78–2.36, P < 0.001). Conversely, factors negatively associated with PrEP use included experiencing food insecurity (0.65, 0.58–0.72, P < 0.001) and housing instability in the past year (0.59, 0.50–0.70, P < 0.001). Compared to those who did not use methamphetamine in the past two years, participants who stopped methamphetamine use were less likely to use PrEP (0.83, 0.70–0.98, P = 0.025), those who initiated methamphetamine were more likely to use PrEP (1.47, 1.16–1.85, P = 0.001), and those who used methamphetamine persistently had equal likelihood of using PrEP (0.85, 0.69–1.05, P = 0.132). Race/ethnicity was not associated with PrEP uptake in the bivariate analyses.

Table 2 Bivariate GEE model results of individual characteristics and PrEP uptake among sexual and gender minority people in a U.S.-based longitudinal cohort, *Together 5,000*, 2017–2022

Predictors	Crude Odds Ratios	95% CI	*P* value
Time points vs. 12 months			
24 months	1.36	1.26–1.47	**< 0.001**
36 months	1.68	1.54–1.82	**< 0.001**
48 months	2.13	1.95–2.32	**< 0.001**
bs(age)1	8.83	3.40-22.97	**< 0.001**
bs(age)2	1.89	1.19-3.00	**0.007**
bs(age)3	3.87	2.11–7.10	**< 0.001**
Racial/ethnic minority vs. non-Hispanic White			
Non-Hispanic Black	0.99	0.81–1.21	0.936
Hispanic/Latinx	1.05	0.92–1.21	0.447
Other	1.09	0.92–1.30	0.314
Food insecure vs. food secure	0.65	0.58–0.72	**< 0.001**
Unstable vs. stable housing	0.59	0.50–0.70	**< 0.001**
Clinically indicated vs. not indicated for PrEP	2.63	2.32–2.98	**< 0.001**
Had health insurance vs. no health insurance	2.40	2.10–2.75	**< 0.001**
Had vs. no PrEP use history	2.05	1.78–2.36	**< 0.001**
Methamphetamine use vs. non-methamphetamine use in the past two years			
Quit methamphetamine	0.83	0.70–0.98	**0.025**
Initiated methamphetamine	1.47	1.16–1.85	**0.001**
Persistently used methamphetamine	0.85	0.69–1.05	0.132

Note "GEE" refers to generalized estimating equation; CI refers to confidence interval. The results are unweighted. GEE model assumes an independent working correlation structure

Multivariable Results of Predictors of PrEP Use

Table 3 presents the results of an observation-weighted multivariable GEE model with 16,949 person-years. Results from the multivariable analysis mirrored the bivariate analyses, except for race/ethnicity and quitting methamphetamine, the former became statistically significant in multivariable model and the latter became non-significant. Specifically, compared to White individuals, Hispanic/Latinx individuals were more likely to use PrEP (adjusted OR [aOR]: 1.19, 1.03–1.37, P = 0.016), controlling for other demographic, socio-economic, and behavioral factors. Factors associated with PrEP use were older age (25–34 vs. 15–24 age group: 1.24, 1.06–1.44, P = 0.008; 35–44 vs. 15–24 age group: 1.22, 1.02–1.46, P0.026; Supplemental Table S1), being clinically indicated for PrEP (2.83, 2.48–3.22, P < 0.001), having health insurance (2.25, 1.96–2.59, P < 0.001), and a history of PrEP use (1.99, 1.72–2.30, P < 0.001). Conversely, factors negatively associated with PrEP use included experiencing food insecurity (0.76, 0.68–0.85, P < 0.001) and housing instability (0.76, 0.62–0.93, P = 0.008) in the past year. Compared to those who did not use methamphetamine in the past two years, those who initiated methamphetamine were more likely to use PrEP (1.58, 1.22–2.05, P = 0.001), and those who quit methamphetamine (1.01, 0.85–1.21, P = 0.890) and those who used methamphetamine persistently (0.94, 0.75–1.18, P = 0.595) had equal likelihood of using PrEP. The GEE model assumed an independent working correlation structure, and the results were robust in the multivariable GEE model without weighting (Supplemental Table S2).

Table 3 Multivariable, observation-weighted GEE model results for PrEP use among sexual and gender minority individuals in a U.S.-based longitudinal cohort, *Together 5,000*, 2017–2022

Predictors	Adjusted Odds Ratios	95% CI	*P* value
Time points vs. 12 months			
24 months	1.38	1.27–1.49	**< 0.001**
36 months	1.77	1.62–1.95	**< 0.001**
48 months	2.08	1.88–2.29	**< 0.001**
bs(age)1	3.42	1.26–9.30	**0.016**
bs(age)2	1.51	0.94–2.44	0.090
bs(age)3	1.84	0.97–3.48	0.063
Racial/ethnic minority vs. non-Hispanic White			
Non-Hispanic Black	1.10	0.90–1.35	0.352
Hispanic/Latinx	1.19	1.03–1.37	**0.016**
Other	1.14	0.95–1.36	0.163
Food insecure vs. food secure	0.76	0.68–0.85	**< 0.001**
Unstable vs. stable housing	0.76	0.62–0.93	**0.008**
Clinically indicated vs. not indicated for PrEP	2.83	2.48–3.22	**< 0.001**
Had health insurance vs. no health insurance	2.25	1.96–2.59	**< 0.001**
Had vs. no PrEP use history	1.99	1.72–2.30	**< 0.001**
Methamphetamine use vs. non-methamphetamine use in the past two years			
Quit methamphetamine	1.01	0.85–1.21	0.890
Initiated methamphetamine	1.58	1.22–2.05	**0.001**
Persistently used methamphetamine	0.94	0.75–1.18	0.595

Note: "GEE" refers to generalized estimating equation; CI refers to confidence interval. 4,942 participants were included in the analysis with 16,949 person-years. The results are weighted with inverse probability of censoring weighting. GEE model assumes an independent working correlation structure

Discussion

This U.S. national, longitudinal, observational study conducted over a 4-year period among SGMSM provides crucial insights into real-world PrEP uptake, its progress, and key influencing factors, including those that can be modified for HIV prevention. We examined methamphetamine use, a key driver of HIV infection in SGMSM populations. The annual rate of PrEP uptake increased over the 4-year follow up, but the prevalence of use remained low—with only 37.1% of participants reporting having used PrEP. This finding is consistent with the National HIV Behavioral Surveillance (NHBS), which reported that 35% of cisgender MSM aged 18 and above who were clinically indicated for PrEP were using it [26].

Our study findings indicated that individuals who initiated methamphetamine use were more likely to use PrEP, even after accounting for other factors. This finding is consistent with our first hypothesis and suggests that the participants who were most vulnerable to HIV due to recent methamphetamine use are, indeed, adopting PrEP—potentially mitigating their heightened vulnerability. Conversely, participants who ceased methamphetamine use were less likely to be on PrEP, as seen in our bivariate results, which is also consistent with our hypothesis. However, after adjusting for other variables, this effect did not persist in our multivariable analysis, which is inconsistent with our second hypothesis. Although discontinuing methamphetamine use reduced one risk factor for HIV seroconversion, it did not eliminate all behaviors that potentially increase individuals' vulnerability to HIV. Therefore, integrating HIV screening and PrEP education with substance use interventions could be a critical opportunity for increasing PrEP uptake among populations exhibiting behaviors associated with increased HIV risk, such as prior methamphetamine use. Given that HIV seroconversions frequently occur shortly after PrEP discontinuation [27], this finding underscores a critical HIV prevention opportunity. Notably, individuals with persistent methamphetamine use exhibited a similar likelihood of PrEP use as non-users, contrary to our hypothesis of increased PrEP uptake. Given the exceptionally high HIV risk associated with methamphetamine use [11], one would expect a higher likelihood of PrEP use in this group. It is also likely that persistent meth users who perceived a need for PrEP and used it due to meth use would have been screened out of the study. Therefore, the relationship between persistent meth use and PrEP use needs to be further explored in future studies. Our findings underscore the importance of addressing methamphetamine use and its connection to PrEP uptake as part of efforts to end the HIV epidemic [28]. Our findings generally align with extant literature, indicating that those initiating methamphetamine use leverage the biological protection offered by PrEP. However, the equal or lower likelihood of PrEP use among persistent methamphetamine users or quitters raises concerns and necessitates the development of novel intervention strategies to optimize PrEP uptake and engagement in SGMSM populations, particularly among individuals who persistently use or quit methamphetamine. There is a growing literature on combination interventions that co-target HIV-related health behaviors and substance use or mental health symptoms, yet more work is needed [29].

Our findings are consistent with existing literature regarding the impact of housing instability, food insecurity, health insurance, clinical indication for PrEP, and prior history of PrEP use on PrEP uptake [30–32]. Our results emphasize the importance of addressing basic needs such as stable housing and food security as critical factors in facilitating PrEP uptake and HIV prevention, in line with WHO recommendations [33]. To overcome barriers such as lack

of health insurance and high out-of-pocket costs associated with PrEP, it is crucial to establish partnerships and effective communication between medical and social service providers. This would help uninsured or underinsured individuals at high risk of acquiring HIV have access to free or affordable PrEP medication through programs such as the U.S. government's "Ready, Set, PrEP" initiative, Gilead's Advancing Access Program, and various state health programs [34, 35]. Our findings suggest that PrEP implementation programs should consider incorporating screening for and addressing social determinants of health (e.g., basic needs of food and housing, health insurance coverage) as an important strategy to improve PrEP uptake and overall health of SGMSM communities [36]. Strategies are needed to assist those who may benefit from PrEP but are currently not receiving PrEP, especially reaching those who have never used PrEP.

Although it is well-established that older age is associated with higher PrEP uptake, our study yielded a unique finding regarding the relation between race/ethnicity and PrEP use. In contrast to existing literature, we observed that Hispanic/Latinx individuals were more likely to use PrEP than White individuals, after controlling for other variables. This discrepancy may be attributed to our recruitment strategy and its timing, which specifically targeted individuals being clinically indicated for PrEP but not currently taking it. Consequently, White individuals, who tend to have higher rates of PrEP use (i.e., many have already adopted PrEP) [37], were more likely to be excluded from our study. Our screening data further supported this observation, revealing that among individuals screened but not included in the study, White individuals had the highest rate of PrEP use (Supplemental Table S3). Therefore, it is plausible that the White individuals included in our study were late adopters of PrEP, and characteristically distinct from those early adopters—an area for future research.

Limitations

Our findings should be understood in light of their limitations. Firstly, the generalizability of our findings to all SGMSM is limited because we specifically recruited participants who were at substantial vulnerability to HIV based on their sexual risk behaviors and PrEP use status. Secondly, to mitigate potential bias introduced by frequent interactions with research measures and staff, which can influence participant behaviors (i.e., the Hawthorne Effect) [38], we designed our study to be conducted online and assessed annually with minimal contact from study staff. However, the infrequency of assessments limited the granularity of our data. For instance, individuals who used meth within the last month, but might have stopped at any point in the previous 11 months, are still categorized as persistent users due to our inability to distinguish them from those who used meth continuously in our annual assessments. In another example, while we assessed current PrEP use, we lacked information on the duration of PrEP use, which limits our understanding about PrEP persistence.

In addition, our measurement of methamphetamine use was dichotomous over a long recall period. Although we captured changes in use over the past two years, we acknowledge that methamphetamine use can vary seasonally within individuals, and that granularity was not captured in our study and should be further explored in future research. Furthermore, our adaptation of the CDC's 2017 criteria for clinical indication for PrEP, which excluded factors such as commercial sex work, may have led to underestimating the percentage of participants eligible for PrEP. We acknowledge that, according to the broader 2021 guidelines, the proportion of participants indicated for PrEP could be higher than what we have reported. Notably, our findings indicate that over three-quarters of participants were consistently eligible for PrEP at each follow-up, suggesting a potential underestimation in our study.

With the exception of HIV seroconversion, all other measures in our study were self-reported, which may be subject to social desirability biases. However, such effects could be minimized by our online assessments, vs. face-to-face interviewing [39]. Lastly, while prospective cohort studies allow us to assess measures repeatedly and potentially more accurately than cross-sectional studies, longitudinal retention can be a challenge, particularly in long-term follow-up [40]. To address potential biases from attrition, we utilized inverse probability weights in our multivariable GEE modeling and conducted sensitivity analyses to validate the robustness of our results.

Conclusion

Although PrEP uptake increased over time, the prevalence of PrEP use remained low, with more than three-fifths of SGMSM not using PrEP at all during the 4-year follow up, despite being clinically indicated for PrEP at enrollment and, for many, throughout the duration of the study. The patterns of methamphetamine use were significantly associated with PrEP use. Individuals who initiated methamphetamine were more likely to report using PrEP, while those who quit or persistently used methamphetamine had similar likelihoods of using PrEP as non-users. Given the low prevalence of PrEP uptake and the lasting consequences of HIV seroconversion, urgent measures are needed to remove barriers to PrEP uptake. Healthcare providers conducting HIV testing and/or providing PrEP care to SGMSM individuals

should simultaneously assess for methamphetamine use and make referrals for harm reduction counseling in both sexual behavior and drug use. In addition, immediate action is required to tackle social determinants of health, such as food insecurity, housing instability, and lack of health insurance, along with other risk factors (e.g., younger age, clinical indication for PrEP, meth use), to enhance PrEP use and reduce HIV infections.

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