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Poppers and PrEP: Use of Pre-Exposure Prophylaxis among Men Who Have Sex with Men Who Use Inhaled Nitrites

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Abstract

Men who have sex with men (MSM) commonly use inhaled nitrites, or poppers, though their use is a risk factor HIV seroconversion. Pre-exposure prophylaxis, or PrEP, is effective for HIV prevention, but is not widely used, and little is known regarding PrEP use and acceptability among MSM who use inhaled nitrites. We surveyed 580 MSM in Paris, France in 2016 about popper use, sexual behaviors including condomless anal intercourse (CAI), serosorting, and sexual positioning, PrEP use, PrEP candidacy, and interest in alternate PrEP delivery modalities. We included 444 HIV negative participants for the current study. 46.2% reported popper use in the prior 3 months. Using multivariate adjusted logistic regression, we found that popper users were more likely than non-users to consider themselves candidates for PrEP (adjusted relative risk ratio (aRRR)=2.73; 95% CI=1.54–4.83), but they were not more likely to be current (aRRR=1.54; 95% CI=0.71–3.33) or past (aRRR=1.37; 95% CI=0.44–4.28) PrEP users. Mediation analyses indicated that increased CAI and serosorting partly explained the relationship between popper use and PrEP candidacy.

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There was considerable interest in alternate proposed PrEP delivery modalities, particularly long-acting injectable PrEP (adjusted risk ratio (aRR)=1.43; 95% CI=1.15–1.79).

Keywords

HIV prevention; men who have sex with men; poppers; inhaled nitrites; PrEP

INTRODUCTION

Despite significant progress in HIV prevention and treatment since the recognition of AIDS in the early 1980s, the global burden of disease posed by HIV/AIDS remains unacceptably high. Within developed nations, men who have sex with men (MSM) remain disproportionately affected by HIV, with HIV incidence actually increasing among MSM in many nations, including several in Western Europe (1). As of 2015, the prevalence of HIV among MSM remained over 10% in only three Western European nations: France, Spain, and Belgium (2). In France in particular, while MSM represent only 3.9% of the population (3), they accounted for 38% of all new infections in 2015 (4, 5).

Given that the HIV epidemic disproportionately affects MSM in France, understanding both the individual and societal factors that influence behaviors pertinent to HIV prevention within this population is critical to turn the tide of increasing HIV incidence. Significant work has been done to provide individuals with tools for HIV prevention, including education on safer sex practices, wide dissemination of condoms, recommendations for frequent testing, and pre-exposure prophylaxis (PrEP). The efficacy of PrEP has been proven in two formulations: both a once daily formulation in the global iPrEx (6) and U.K.-based PROUD (7) trials and a peri-coital dosing regimen in the French-based IPERGAY trial (8), in which individuals took two pills before and a pill a day for 2 days after a sexual encounter.

PrEP is now available in France in both daily and on demand dosing regimens; in the first six months following its January 2016 rollout, 1,077 individuals, 96.4% of whom were MSM, began taking PrEP (9). While this number is expected to grow as awareness increases and more providers offer PrEP, concerns regarding side effects (10), cost (11), stigma (12), and difficulties with adherence (13) remain significant barriers to achieving the widespread implementation necessary to decrease HIV incidence. It is therefore useful to identify specific subgroups of MSM whom may be vulnerable to contracting HIV and would thus be ideal candidates for PrEP, such as those who have a large number of partners and those who engage in condomless anal intercourse (CAI). Such is the basis for both the European Clinical AIDS Society and the US Center for Disease Control and Prevention's recommendations that MSM with high numbers of sexual partners, who report a history of CAI, who engage in commercial sex work, or who have a recent bacterial sexually transmitted disease (STD) be offered PrEP (14, 15). Given, however, that social desirability bias may impact patients' willingness to report total numbers of partners and episodes of CAI to their healthcare providers (16–19), other means of risk-stratifying patients could aid in identifying ideal PrEP candidates.

One possible driver of condomless sexual behavior among MSM is the use of inhaled nitrites, commonly known as poppers. Poppers are often used among MSM to enhance desire and pleasure during sex and to facilitate receptive intercourse via smooth muscle relaxant effects (20–22). This is notable given that popper use has been associated with increased rates of group sex (23), condomless anal intercourse (24–26), serodiscordant CAI (24–26), HIV seropositivity (27), undiagnosed HIV infection (28), and having multiple sex partners (27) among samples of MSM individuals in the United States (24, 25, 29), Europe (26, 28), and China (23, 27, 30). Moreover, results from the USA-based Multicenter AIDS Cohort Study of 4003 HIV seronegative men have demonstrated that popper use has been independently associated with a relative hazard of HIV seroconversion ranging from 2.10–3.89 (31, 32), implying a possible prospective association between poppers use and increased susceptibility to HIV, particularly when used in conjunction with other “sex drugs” (e.g., stimulants and erectile dysfunction drugs) (31).

Consistent with these data, in a prior analysis of survey data from 580 geosocial network app-using MSM in Paris, France (33), we found that poppers use was quite prevalent, with nearly half of survey respondents reporting poppers use within the prior three months. In addition, we found that popper users were more likely than non-users to practice CAI, engage in group sex, and report a diagnosis of an STI within the past three months, reaffirming the argument that MSM who use poppers represent a subgroup at higher than average risk for HIV seroconversion, and therefore would be appropriate candidates for PrEP. Nevertheless, we are not aware of any literature that has examined the association of poppers use with attitudes towards PrEP, specifically assessing the extent of PrEP use, knowledge of PrEP, and self-perceived candidacy for PrEP among MSM. We are aware that MSM commonly use other drugs during sex, including stimulants (e.g., methamphetamines, cocaine), and erectile dysfunction medications (e.g., phosphodiesterase inhibitors, injected prostaglandin E₁) (22, 34, 35), and indeed in our prior analysis of this sample (33), MSM who used poppers were more likely to use other drugs or alcohol during sex than those who did not use poppers. Given however the marked prevalence of popper use when compared with other drugs in this sample (46.7% reporting popper use versus 1.6% reporting methamphetamine use, for example) and the relative dearth of literature devoted specifically to popper use, we chose to focus the present analyses on poppers use alone.

METHODS

Sample Recruitment

This study recruited potential participants via broadcast advertisements on a popular geosocial-networking smartphone application used by MSM to meet romantic and sexual partners. These advertisements were targeted to users of this application located in the Paris, France metropolitan area in October 2016. Users were shown an advertisement with text (in both English and French) encouraging them to click through the advertisement to complete an anonymous web-based survey. The advertisements were shown to users during three consecutive 24-hour periods on the first instance a user logged onto the application in a 24-hour period. While users could have potentially seen the advertisement multiple times, precautions (e.g., use of the “Prevent Ballot Box Stuffing” feature on Qualtrics) were taken

to avoid and eliminate duplicate responses, as done in previous research (36). No duplicate responses were apparent.

Our survey, which included 52 items, was translated from English into French using an adaptation of the TRAPD (translate, review, adjudicate, pretest, document) model (37). The survey was translated by three native French speakers, and then reviewed and adjudicated by a fourth native French speaker. Finally, the survey was pretested through back-translation by a fifth French speaker and health researcher, yielding its final form. The survey took an average of 11.4 minutes (SD = 4.0) for users to complete. The survey was offered in French and English; 94.3% took the survey in French. At the end of the recruitment period (i.e., three 24-hour periods), 5,206 users had clicked on the advertisement and reached the landing page of the survey, 935 users provided informed consent and began the survey, and 580 users completed the survey, representing an overall response rate of 11.1%. All protocols were approved by the New York University School of Medicine Institutional Review Board prior to data collection. All respondents reported being at least 18 years old at the time of survey administration.

Measures

HIV Status—Participants were asked to self-report their HIV status with one item reading “What is your HIV status?” with three response options (negative, positive, and unknown). Only participants who reported being HIV negative were included for this analysis, given its focus on a prevention modality indicated only for HIV-negative individuals.

Condomless Anal Intercourse—Participants indicated the number of partners with whom they had engaged in condomless insertive anal intercourse and condomless receptive anal intercourse in the preceding three months. These count variables were transformed into categorical variables with two categories (0 partners and 1 or more partners) for each role and for the combined measure for the purposes of these analyses.

Serosorting—Participants were asked “In the past three months, did you ever practice anal intercourse without a condom, having previously asked your partner if he was of the same HIV status as you, in order to prevent HIV infection?” with response options “Yes” and “No”.

Sexual Positioning—Participants were asked “In the past three months, did you ever practice anal intercourse without a condom and choose only the insertive or receptive role in order to prevent HIV infection?” Response options were “Yes, only receptive anal intercourse,” “Yes, only insertive anal intercourse,” and “No”. For the purposes of these analyses, responses were dichotomized into “Yes” and “No”.

Use of Poppers and other Drugs—To assess substance use, participants were asked “In the past three months, have you used any of the following?” with possible responses including cigarettes, electronic cigarettes, alcohol, marijuana, synthetic cannabinoids, cocaine, MDMA, ketamine, GHB/GBL, heroin, methamphetamine, prescription amphetamines, prescription benzodiazepines, inhalant nitrites, other inhalants, prescription opioids, psychedelics, new psychedelics, synthetic cathinones, and steroids. As discussed

above, for the purposes of this analysis, we examined only the use of inhalant nitrites within the past 3 months.

Use of Daily Oral Pre-Exposure Prophylaxis—PrEP-related measures were adapted from recent studies in the literature (38, 39). Respondents were given the following description of once daily PrEP, “Pre-exposure prophylaxis (PrEP) is a new prescription medication that can be taken by an HIV-negative person to protect against HIV. It is sometimes referred to by the brand name Truvada. Currently, it is available in the form of a pill taken once every day.” Participants were asked if they had ever heard of once daily PrEP to prevent HIV infection before taking the survey. Participants were also then asked if they had ever taken PrEP and if they were currently taking PrEP. Participants were then given the following statement, “Once daily PrEP has been shown to be at least 90% effective in preventing HIV when taken daily,” and then asked, “How likely would you be to take this form of PrEP in the future?” Respondents answered this item on a five point Likert scale ranging from “Very unlikely” (1) to “Very likely” (5). Responses for likelihood were recoded into unlikely/undecided to use once daily PrEP (very unlikely, unlikely and undecided) and likely to use once daily PrEP (very likely and likely combined).

Perceived Candidacy for PrEP—Participants were asked the question “Do you believe that you are currently an appropriate candidate for PrEP?” Response options were “Yes, I am definitely an appropriate candidate”, “I’m not sure who is an appropriate candidate”, and “No, I am definitely not an appropriate candidate”.

Likelihood to Use Event-Driven Pre-Exposure Prophylaxis—Respondents were given the following description of event-driven PrEP, “Scientists are testing the effectiveness of taking PrEP based on when someone has sex. Users of this type of PrEP would not need to take it when they are not having sex. It would involve taking four pills – two pills taken within 24 hours before sexual activity and two separate one-pill doses within two days after sex. Scientists believe that this can work similarly to daily PrEP to prevent HIV. This is called ‘event-driven PrEP.’” Participants were then given the following statement, “Suppose that event-driven PrEP is at least 90% effective in preventing HIV when used as described previously” and then asked, “How likely would you be to take this form of PrEP in the future?” Respondents answered this item on a Likert scale ranging from “Very unlikely” (1) to “Very likely” (5). Responses for likelihood were recoded into unlikely/undecided to use once daily PrEP (very unlikely, unlikely and undecided) and likely to use once daily PrEP (very likely and likely combined).

Likelihood to Use Long-Acting Injectable Pre-Exposure Prophylaxis— Respondents were given the following description of long-acting injectable PrEP, “Scientists are also working to make a different kind of PrEP that would not require taking a pill every day. Instead, it would involve getting an injection once a month and would not require a daily pill. Scientists believe that this new injection could work similarly to daily oral PrEP to prevent HIV, but conclusive results have not yet been obtained. This is called ‘long-acting injectable PrEP.’” Participants were then given the following statement, “Suppose that long-acting injectable PrEP is at least 90% effective in preventing HIV when injected every

month”, and then asked, “How likely would you be to take this form of PrEP in the future?” Respondents answered this item on a Likert scale ranging from “Very unlikely” (1) to “Very likely” (5). Responses for likelihood were recoded into unlikely/undecided to use once daily PrEP (very unlikely, unlikely and undecided) and likely to use once daily PrEP (very likely and likely combined).

Likelihood to Use Topical Microbicides—Respondents were given the following description of topical microbicides, “Microbicides are products that are applied directly to the penis or the rectum prior to sex to prevent the transmission of HIV. They come in the form of a gel, cream, or suppository. A number of these products are currently being tested around the world to see if they are effective.” Participants were then given the following statements “Suppose a microbicide was at least 90% effective in preventing HIV as a gel applied to the penis,” and “Suppose a microbicide was at least 90% effective in preventing HIV as a gel applied to the rectum,” and then asked, “How likely would you be to use it the future?” for both rectal and penile microbicides respectively. Respondents answered these items on a Likert scales ranging from “Very unlikely” (1) to “Very likely” (5). Responses for likelihood were recoded into unlikely/undecided to use once daily PrEP (very unlikely, unlikely and undecided) and likely to use once daily PrEP (very likely and likely combined).

Preferences for Pre-Exposure Prophylaxis Administration Modalities—

Respondents were then asked, “Given the choice between these different forms of prevention, which would you prefer to use?” with the following answer choices: once daily PrEP, event-driven PrEP, long-acting injectable PrEP, microbicide applied to the penis, microbicide applied to the rectum, whichever form is most effective, I have no preference, and none of these prevention strategies.” Each response option was then dummy coded for use as an outcome variable in multivariate analyses with the response category being the selection the specified administration method (e.g., once daily pills) and the reference category being the selection of all other response options to this question.

Socio-Demographic Characteristics—Participants were asked to report their age (in years), sexual orientation (response options: gay, bisexual, straight, other), whether or not they had been born in France (response options: yes, no), employment status (response options: employed, unemployed, student, retired), and current relationship status (response options: single, relationship with a man, relationship with a woman). Certain categories of variables (i.e., straight, other, retired and relationship with a woman) were not taken into account in the analyses due to low prevalence. The continuous variable of age was categorized into 5 groups: 18–24, 25–29, 30–39, 40–49, 50 years and older.

Analyses

All analyses were conducted in Stata Version 14.0 (StataCorp, College Station, Texas, USA). Analyses were partly informed by the framework of the behavioral model for vulnerable populations (40). The health behavioral model (41) posits that health behaviors, a major determinant of health outcomes, are determined by three population-level domains: predisposing factors (demographics, health beliefs, and social structures), enabling factors (personal/family and community resources, such as access to healthcare) and need-related

factors (perceived and evaluated health). The model was revised in 2000 by Gelberg et al. to include attention to the unique structural barriers encountered by vulnerable populations, including sexual minorities (40). In the context of this framework, we assessed for predisposing factors including age, sexual orientation, employment status, and relationship status, and need-related factors including perceived candidacy for PrEP in an effort to measure the relationship between popper use and health behaviors of interest – in this case, PrEP use and likelihood to use other PrEP formulations. We did not specifically assess for enabling factors given the context of universal healthcare and open access to PrEP in France (42).

In undertaking the analysis, first, we calculated descriptive statistics for all study variables. We excluded all participants who did not report HIV-negative serostatus. Then, the demographic and behavioral characteristics of MSM who used poppers were compared to those who did not using chi-square statistics. Missing values were handled in Stata by listwise deletion. For dichotomous outcomes (“very unlikely”, “unlikely”, or “undecided” = 0; “likely” or “very likely” = 1), we used a log-binomial regression model to estimate the relative likelihood of popper users to report themselves as likely to use individual PrEP modalities (once daily oral PrEP, on-demand PrEP, long-acting injectable PrEP, penile microbicide PrEP, and rectal microbicide PrEP) when compared with non-users. We also used a log-binomial regression model to compare the relative likelihood of popper users to prefer a given PrEP modality in comparison with non-users. When convergence problems occurred with log-binomial model, we used a modified Poisson regression model, which combines a log Poisson regression model with a robust error variance. This model has been suggested as a useful alternative to log-binomial regression for estimating relative risks (43–45). The adjusted relative risk (aRR) and 95% confidence intervals were presented. To evaluate popper use in association with trichotomous outcomes (current, past, or no PrEP use, and perceived PrEP candidacy), a multinomial logistic regression model was used to determine adjusted relative risk ratios (aRRRs). Adjusted models controlled for sociodemographic characteristics, including age, sexual orientation, place of birth, employment, and current relationship status. Finally, we conducted a mediation analysis to examine whether the relationship between popper use and PrEP candidacy was mediated by condomless anal intercourse, serosorting, or sexual positioning. Using the approach of Valeri & VanderWeele (paramed command in Stata) (46, 47), we calculated natural direct effect (NDE), natural indirect effect (NIE) and marginal total effect (MTE) with bootstrapped bias-corrected 95% confidence intervals. The same set of covariates were included in the analyses. Mediation was considered significant if the natural indirect effect was significant at $\alpha=0.05$ level.

RESULTS

Sample characteristics

Table I summarizes the sample characteristics. Of 580 MSM, 444 were HIV negative and included for this study. Among 444, approximately half of the respondents (46.2 %) reported that they had used poppers in the previous 3 months. While most respondents (87.2%) were aware of PrEP, PrEP use was not highly prevalent; only 32 respondents (7.2%) reported

current use, with an additional 14 (3.2 %) reporting past use. Despite this, 26.4% of the sample reported themselves as “definitely” an appropriate candidate, while 46.2% reported being “not sure” as to who is an appropriate candidate. Respondents in general reported themselves as likely or very likely to use multiple proposed PrEP modalities, including on-demand oral (45.1%), long-acting injectable (43.7%), penile microbicide gel (50.9%), and rectal microbicide gel formulations (55.2%). Long-acting injectable PrEP was the most popular individual option for PrEP delivery (20.7%), after “whichever formulation is most effective” (32.4%).

PrEP Use, Perceived PrEP Candidacy, Sexual Behaviors, and Likelihood to Use PrEP Modalities Among Popper users

Multivariate associations are presented in Tables II–IV. In the adjusted multinomial logistic regression analysis, MSM who used poppers were more likely to perceive themselves as candidates for PrEP (adjusted relative risk ratio (aRRR) = 2.73; 95% CI = 1.54–4.83) (Table II). Despite this, popper users were not significantly more likely to be past (aRRR = 1.37; 95% CI = 0.44–4.28) or current (aRRR = 1.54; 95% CI = 0.71–3.33) PrEP users than non-popper users (Table II), though overall PrEP use was low. Regarding sexual behaviors relevant to HIV risk, popper users were significantly more likely to engage in condomless anal intercourse (CAI) (aRR = 1.30; 95% CI = 1.01–1.67) and serosorting (aRR = 1.24; 95% CI = 1.02–1.52), but not in strategic sexual positioning (aRR = 15.0, 95% CI = 0.89–2.53). Notably among unadjusted analyses, MSM who were born in France were significantly less likely to consider themselves candidates for PrEP as MSM who were not born in France (RR = 0.43, 95% CI = 0.21–0.87; Table II).

Compared to those who had not used poppers in the past 3 months, those who had used poppers in the past 3 months were more likely to report themselves as “likely” or “very likely” to use multiple PrEP modalities, including long-acting injectable PrEP (aRR = 1.43; 95% CI = 1.15–1.79) and penile microbicide PrEP (aRR = 1.28; 95% CI = 1.06–1.53), but not once daily oral PrEP (aRR = 1.28; 95% CI = 1.00–1.65), on-demand oral PrEP (aRR = 1.09; 95% CI = 0.90–1.33), or rectal microbicide PrEP (aRR = 1.19; 95% CI = 1.00–1.41) (Table IV). When asked which PrEP modality they would most prefer, popper users were significantly more likely to prefer long-acting injectable PrEP (aRR = 1.51; 95% CI = 1.04–2.21) when compared with non-users (Table IV).

Mediation analyses

The results of mediation analysis are presented in Table V. Natural direct effect, natural indirect effect and total effects of the mediation pathways were estimated. Serosorting, CAI, and sexual positioning were considered as possible mediators in the association between popper use and PrEP candidacy; however, as sexual positioning was not significantly associated with popper use (Table III), this could not be assessed as a candidate mediator. We found that both serosorting and CAI partially mediated the association of popper use with PrEP candidacy, with a significant natural indirect effect of serosorting and CAI on PrEP candidacy (RR_{NIE} = 1.13; 95% CI = 1.02–1.36, RR_{NIE} = 1.10; 95% CI = 1.00–1.26, respectively).

DISCUSSION

Although popper use has been shown to be highly correlated with HIV seropositivity, due to both high rates of sexual risk behavior (24–26, 33) and direct vasodilatory effects of inhaled nitrites (32), we found that popper users were not more likely to be using PrEP than non-popper users. Indeed, while 26.4% of popper users reported themselves as “definitely” an appropriate candidate for PrEP, only 7.2% reported current PrEP use. Moreover, while popper users in our sample were significantly more likely than non-users to consider themselves appropriate candidates for PrEP, they were not significantly more likely to be current or past PrEP users. In this context, it is notable that the relationship between popper use and PrEP use was partially mediated by condomless anal sex (CAI) and serosorting. This implies that additional risk-taking (CAI) or risk-reduction strategies (serosorting) may partially influence whether an individual who uses poppers views himself as a candidate for PrEP. For example, MSM who use poppers and engage in CAI may perceive of themselves at particularly high risk of HIV seroconversion, and therefore as candidates for PrEP, though notably increased rates of CAI did not fully account for the relationship between popper use and PrEP candidacy. On the other hand, given that increased levels of serosorting explained part of the relationship between popper use and PrEP candidacy, it could be that MSM who engage in some form of HIV risk reduction are more cognizant of their risk at baseline, and are therefore more likely to view themselves as PrEP candidates.

Regarding the observed discordance between PrEP candidacy and uptake, there are multiple potential barriers that may explain this difference. A discussion of these may be clarified with reference to the “PrEP care continuum,” a conceptual framework designed to organize the steps necessary for PrEP uptake and adherence (48): (1) identifying a population at risk of HIV seroconversion, (2) promoting PrEP awareness, (3) ensuring willingness to use PrEP, (4) ensuring healthcare access, (5) ensuring prescription coverage of PrEP, and (6) promoting ongoing adherence.

Considering each step in the PrEP care continuum in turn, popper users clearly constitute an at-risk population who would benefit from PrEP based on the European AIDS Clinical Society Guidelines (14). Despite this, given that PrEP has only been available in France since January 2016 (49), nine months prior to our survey, French medical providers may not have been screening all patients at-risk and recommending PrEP to all those who would benefit, as has been the case in the USA: while PrEP was approved by the FDA in 2012, as of 2014–15, only 28% of US primary care providers felt comfortable prescribing PrEP (50). Ongoing education of medical providers in France of the safety and efficacy of PrEP may therefore be warranted to promote PrEP uptake, particularly given the outstanding access to healthcare enjoyed by French citizens (51) and the full approval of PrEP funding by the European Medicines Agency in July 2016 (42). Indeed, this study is notable in part because in contrast to the USA, where access to PrEP is not universal and low PrEP uptake in America may be partly explained by barriers to access, PrEP use was sub-optimal in this sample despite widespread access. That is, addressing structural barriers within the PrEP cascade is a necessary but not sufficient, step to optimizing PrEP uptake and adherence.

Regardless of providers' behaviors, a lack of knowledge about PrEP is unlikely to explain poor PrEP uptake in our sample given that 87% of respondents and nearly 90% of popper users reported having heard about PrEP prior to survey administration. Clearly, however, knowledge of PrEP and willingness to use it are separate, and indeed only 37.6% of HIV-negative survey respondents reported themselves as "likely" or "very likely" to use oral PrEP in the future. Though popper users were more open to use oral PrEP than non-users (aRR=1.28), still less than half of popper users surveyed reported themselves as "likely" or "very likely" to use once daily oral PrEP, the only PrEP formulation currently available. In viewing these results in the context of the health behavior model (40, 41), this reinforces the idea that the forces driving behavior relevant to sexual health include not only health beliefs (e.g., PrEP candidacy) and healthcare availability in general but also sociocultural forces including stigma (12) and the dynamics of the patient-provider relationship (e.g., did the provider screen appropriately for sexual risk behavior, and if so, was PrEP offered?). Notably, in a 2017 analysis by Parsons et al. (52) of PrEP uptake among MSM in the USA using the transtheoretical model of behavior change, 53% of respondents who met CDC criteria for PrEP candidacy were in the "precontemplation" stage of change, i.e., either did not consider themselves a candidate or were unwilling to use PrEP regardless of candidacy, and another 23% were in the "contemplative" stage, implying they were open to the idea of PrEP but had yet to take any steps to begin using it. These findings mirror our findings of substantial disparity between PrEP awareness and use and reinforce the fact that providers should be proactive in engaging MSM in PrEP counseling to encourage MSM who are willing to use PrEP to actually take it and to educate and motivate MSM who are objective PrEP candidates but are presently opposed to the idea of using it. This is particularly relevant in light of the fact that MSM born in France were significantly less likely to consider themselves candidates for PrEP than those who were born elsewhere, perhaps owing to the relatively recent approval of PrEP by the French health system at the time of this survey in October 2016.

While we did not query users regarding their reasons for using or not using PrEP, it is interesting to note that there was considerable interest in our sample for PrEP modalities other than once daily PrEP, including long-acting injectable and microbicide gel formulations. Of particular note is that popper users were significantly more likely to prefer long-acting injectable (LAI) PrEP when compared with non-users, perhaps due to the ease of adhering to a less frequent dosing schedule (53), or perhaps because of a perception of long-acting drug as providing more consistent, reliable protection (53), though we did not explore respondents' rationale for preferring one agent over another. Regardless of the reason, this finding is consistent with research among MSM in both the USA (53–57) and China (58) that many MSM favor LAI PrEP over oral PrEP, particularly those with a high degree of self-perceived risk, like popper users in our sample, whom perceived themselves as candidates for PrEP at higher rates than non-users. These findings, in conjunction with the reality that popper users often engage in condomless anal intercourse, imply that additional resources directed towards investigation of novel PrEP formulations are warranted, as currently available HIV prevention strategies are insufficient to meet the needs of this high-priority community. However, efficacy trials of these newer HIV prevention modalities are only currently underway, such that they will not be available for several years if they are

proven to be efficacious (53, 59). Thus, for the near term, French public health officials and clinicians need to increase awareness among MSM of the benefits that oral PrEP can provide in decreasing their HIV risk.

Study Limitations

This study is subject to limitations. We obtained self-reported data on popper use, PrEP use, and PrEP preferences among a sample of geosocial network app-using MSM in France. As such, these findings may not be generalizable to MSM outside of Western Europe or MSM who do not use these applications. As with all self-reported data, social desirability bias may have skewed our results; e.g., MSM may have under-reported drug use or over-reported willingness to use PrEP. Recall bias could also be at play if MSM who used poppers were reminded of sexual risk behaviors by that question and more likely to consider themselves appropriate candidates for PrEP. In addition, as with any observational study, the associations reported herein must be interpreted with the caveat that it is impossible to draw causal inferences from the data provided; while we adjusted for several covariates, residual confounding is likely present, and we do not purport to claim that popper use is the main factor driving PrEP use or PrEP preferences, but rather that it is a common practice among MSM that should be considered among many in the complex field of HIV prevention. Moreover, as we examined the association between popper use and several different PrEP modalities and risk ratios were small, our finding that popper users were more likely to prefer long-acting injectable PrEP could be a product of family-wise bias; future research could therefore explore whether or not this association persists among other samples of popper-using MSM. Regarding our finding that popper users were not significantly more likely to use PrEP than non-users, it is notable that there was a trend towards increased PrEP use among this population; the low degree of overall PrEP use in our sample may suggest that our study lacked sufficient power to answer this question. Moreover, in an attempt to avoid survey fatigue, we did not query participants regarding many predisposing, enabling, and need-based factors that may influence PrEP uptake and adherence, including perceived behavioral control over health (60), perceived support from partners regarding PrEP use (60, 61), or specific reasons for preferring not to use PrEP, such as PrEP stigma (12, 62–64) or the long-term health effects of antiretroviral use (54, 62, 63). Moreover, the health behavioral model is only one proposed paradigm for analyzing the factors that predispose to behaviors relevant to sexual health. Fisher's information-motivation-behavioral skills model (65), for instance, has been used to study HIV-relevant preventive behaviors (66–68), though as we did not specifically assess for behavioral skills such as self-efficacy in seeking preventive behaviors in our survey, the applicability of this model to our data would be limited.

Future Research

The marked prevalence of popper use in this sample, coupled with our finding that many poppers users perceive themselves as candidates for PrEP, should prompt further investigations to assess the extent to which MSM who use poppers are aware of the potential dangers of using inhaled nitrites, including an increased risk of HIV seroconversion, and the extent to which this informs their HIV prevention-related behavior. It would also be useful to know to what degree healthcare professionals, particularly those in primary care and

infectious disease, are aware of the high prevalence of popper use among MSM, of the risks posed to their users, and of the corresponding utility of screening for popper use among MSM for the purpose of appropriate counseling, including offering PrEP. In addition, given that a chief finding of this study was low PrEP use among poppers users despite widespread access, further research should explore other steps in the PrEP cascade to determine the most important target for intervention: e.g., are doctors in France offering PrEP, and if so, are French MSM accepting that offer? If not, why not: stigma, side effects, inconvenience, or something else? As noted above, this study did not assess for behavioral skills pertinent to sexual health, such as self-efficacy for preventive behaviors or comfort with discussing preventive preferences with partners; future analyses could examine these as predictors of health behavior within the information-motivation-behavioral skills construct (66), for example. In addition, future investigations could explore popper users' specific rationale for preferring one PrEP modality over another, a question our data cannot address. Given as well that 11% of our sample reported they would not want to use any of the proposed formulations, further investigations could also explore HIV prevention modalities not proposed herein, which could help clinicians and researchers design HIV prevention strategies specifically targeted for this high-priority population. Finally, further research is warranted to explore the safety, efficacy, and acceptability of each of these proposed PrEP formulations, both among MSM in general and among popper users.

CONCLUSIONS

Popper use was highly prevalent among this sample of geosocial network app-using MSM in Paris, France, a population with widespread access to PrEP; many popper users in our sample considered themselves appropriate candidates for PrEP. Despite this, PrEP use among popper users was uncommon, suggesting that access to PrEP is a necessary but insufficient step in the pathway to PrEP uptake and adherence. There was considerable interest in alternate PrEP delivery modalities, particularly long-acting injectable PrEP, among popper users. Further research is therefore warranted to explore novel PrEP delivery modalities and HIV prevention strategies for this high-priority group of MSM.

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Table ISelected characteristics and popper use ($N = 444$)

	Total	Popper use		<i>P</i> -value ^a
	n (%)	Yes	No	
Overall	444 (100)	205 (46.2)	239 (53.8)	
Age				0.022
18–24	64 (14.4)	20 (9.8)	44 (18.4)	
25–29	88 (19.8)	51 (24.9)	37 (15.5)	
30–39	131 (29.5)	61 (29.8)	70 (29.3)	
40–49	108 (24.3)	46 (22.4)	62 (25.9)	
50	46 (10.4)	23 (11.2)	23 (9.6)	
Sexual orientation				0.292
Gay	376 (84.7)	176 (85.9)	200 (85.5)	
Bisexual	56 (12.6)	22 (10.7)	34 (14.5)	
Born in France				0.956
Yes	352 (79.3)	163 (79.5)	189 (79.1)	
No	87 (19.6)	40 (19.45)	47 (19.7)	
Employment status				0.056
Employed	304 (68.5)	139 (67.8)	165 (69.0)	
Unemployed	64 (14.4)	37 (18.1)	27 (11.3)	
Student	65 (14.6)	24 (11.7)	41 (17.2)	
Current relationship status				0.096
Single	298 (67.1)	131 (63.9)	167 (69.9)	
Relationship with a man	129 (29.1)	68 (33.2)	61 (25.5)	
Condomless anal intercourse				0.010
No	221 (49.8)	89 (43.4)	132 (55.2)	
Yes	211 (47.5)	111 (54.2)	100 (41.8)	
Serosorting				0.053
No	272 (61.3)	116 (56.6)	156 (65.3)	
Yes	171 (38.5)	89 (43.4)	82 (34.3)	
Sexual Positioning				0.114
No	383 (86.3)	172 (83.9)	211 (88.3)	
Yes	59 (13.3)	33 (16.1)	26 (10.9)	
Knowledge of daily PrEP				0.219
No	57 (12.8)	22 (10.7)	35 (14.6)	
Yes	387 (87.2)	183 (89.3)	204 (85.4)	
PrEP Use				0.473
Never	397 (89.4)	180 (87.8)	217 (90.8)	
Past	14 (3.2)	7 (3.4)	7 (2.9)	
Current	32 (7.2)	18 (8.8)	14 (5.9)	
PrEP Self-Candidacy				0.008

	Total	Popper use		<i>P</i> -value ^a
	n (%)	Yes	No	
Not a candidate	118 (26.6)	44 (21.5)	74 (31.0)	
Not sure who is a candidate	205 (46.2)	93 (45.4)	112 (46.9)	
Yes, I am a candidate	117 (26.4)	67 (32.7)	50 (20.9)	
Likelihood to use daily PrEP				0.038
Very unlikely, unlikely and undecided	275(61.9)	117 (57.1)	158 (66.1)	
Very likely and likely	167 (37.6)	88 (42.9)	79 (33.1)	
Likelihood to use on-demand PrEP				0.311
Very unlikely, unlikely and undecided	240 (54.1)	106 (51.7)	134 (56.1)	
Very likely and likely	200 (45.1)	98 (47.8)	102 (42.7)	
Likelihood to use long-acting injectable PrEP				0.002
Very unlikely, unlikely and undecided	247 (55.6)	99 (48.3)	148 (61.9)	
Very likely and likely	194 (43.7)	106 (51.7)	88 (36.8)	
Likelihood to use penile microbicide				0.036
Very unlikely, unlikely and undecided	213 (48.0)	88 (42.9)	125 (52.3)	
Very likely and likely	226 (50.9)	116 (56.6)	110 (46.0)	
Likelihood to use rectal microbicide PrEP				0.086
Very unlikely, unlikely and undecided	193 (43.5)	81 (39.5)	112 (46.9)	
Very likely and likely	245 (55.2)	123 (60.0)	122 (51.1)	
PrEP Preference				0.127
Once daily	22 (5.0)	14 (6.8)	8 (3.4)	
Event-driven	46 (10.4)	24 (11.7)	22 (9.2)	
Long-acting injectable	92 (20.7)	49 (23.9)	43 (18.0)	
Penile Microbicide	37 (8.3)	13 (6.3)	24 (10.0)	
Rectal Microbicide	27 (6.1)	10 (4.9)	17 (7.1)	
Most effective	144 (32.4)	63 (30.7)	81 (33.9)	
No preference	18 (4.1)	11 (5.4)	7 (2.9)	
None	55 (12.4)	21 (10.2)	34 (14.2)	

^aChi-square statistic

Table IIAssociations^a of popper use with self-perceived candidacy for PrEP and PrEP use (N=444)

	Self-perceived candidacy for PrEP ^b		PrEP use ^c	
	Not sure	Yes	Past PrEP use	Current PrEP use
	aRRR (95% CI)	aRRR (95% CI)	aRRR (95% CI)	aRRR (95% CI)
Popper use	1.55 (0.95, 2.56)	2.73 (1.54, 4.83)**	1.37 (0.44, 4.28)	1.54 (0.71, 3.33)
Age				
18–24	1.11 (0.41, 2.99)	1.12 (0.35, 3.59)	0.21 (0.01, 2.92)	0.14 (0.01, 1.69)
25–29	1.00 (0.50, 2.03)	0.96 (0.43, 2.16)	0.59 (0.13, 2.73)	0.86 (0.29, 2.56)
30–39	REF	REF	REF	REF
40–49	0.81 (0.43, 1.53)	1.23 (0.60, 2.50)	0.61 (0.15, 2.44)	1.49 (0.62, 3.61)
50	0.72 (0.31, 1.66)	0.46 (0.15, 1.38)	--	0.27 (0.03, 2.15)
Sexual orientation				
Gay	1.04 (0.48, 2.25)	1.00 (0.41, 2.46)	0.77 (0.16, 3.79)	4.37 (0.56, 33.89)
Bisexual	REF	REF	REF	REF
Born in France	0.77 (0.39, 1.51)	0.43 (0.21, 0.87)*	0.63 (0.18, 2.20)	8.81 (1.14, 67.98)
Employment status				
Employed	REF	REF	REF	REF
Unemployed	1.01 (0.50, 2.05)	0.83 (0.37, 1.88)	1.78 (0.44, 7.32)	1.20 (0.42, 3.44)
Student	1.55 (0.60, 4.03)	1.05 (0.35, 3.21)	2.00 (0.26, 15.64)	1.65 (0.26, 10.63)
Current relationship status				
Single	REF	REF	REF	REF
Relationship with a man	0.83 (0.50, 1.40)	0.70 (0.38, 1.28)	1.04 (0.31, 3.56)	1.06 (0.47, 2.35)

^aAdjusted relative risk ratios (aRRRs) with 95 % confidence intervals were calculated using multinomial logistic regression with covariates (age, sexual orientation, origin, employment and relationship status).

^bReference group: those who answered “No, I am definitely not an appropriate candidate for PrEP”

^cReference group: users who had never used PrEP

* p<0.05;

** p<0.01

Table IIIAssociations^a of popper use with serosorting, CAI, and sexual positioning

	Serosorting	CAI	Sexual positioning
	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
Popper Use	1.30 (1.01, 1.67) *	1.24 (1.02, 1.52) *	1.50 (0.89, 2.53)
Age			
18–24	1.42 (0.89, 2.27)	1.25 (0.89, 1.77)	0.70 (0.19, 2.57)
25–29	1.00 (0.70, 1.44)	1.10 (0.83, 1.45)	0.87 (0.37, 2.05)
30–39	REF	REF	REF
40–49	1.08 (0.78, 1.50)	1.07 (0.84, 1.37)	2.19 (1.17, 4.09) *
50	0.85 (0.51, 1.42)	0.77 (0.50, 1.20)	0.78 (0.24, 2.60)
Sexual orientation			
Gay	0.87 (0.61, 1.25)	1.28 (0.89, 1.84)	0.85 (0.39, 1.85)
Bisexual	REF	REF	REF
Born in France	0.97 (0.70, 1.33)	1.31 (0.97, 1.77)	0.77 (0.42, 1.40)
Employment status			
Employed	REF	REF	REF
Unemployed	0.92 (0.64, 1.32)	1.07 (0.82, 1.39)	1.34 (0.71, 2.53)
Student	0.66 (0.40, 1.09)	0.79 (0.54, 1.16)	0.98 (0.32, 2.97)
Current relationship status			
Single	REF	REF	REF
Relationship with a man	0.99 (0.75, 1.30)	1.22 (1.00, 1.49)	1.17 (0.69, 1.97)

^aAdjusted risk ratios (aRRs) with 95 % confidence intervals were calculated using log-binomial regression with covariates (age, sexual orientation, origin, employment and relationship status).

* p<0.05;

** p<0.01

	Once daily PrEP (n=22)	Event-driven PrEP (n=46)	Long-acting injectable PrEP (n=92)	Penile Microbicide (n=37)	Rectal Microbicide (n=27)	Any kind of form is most effective (n=144)	No preference ^b (n=18)	None of these prevention strategies (n=55)
	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)	aRR (95% CI)
Sexual orientation								
50	0.45 (0.06, 3.50)	--	0.57 (0.24, 1.36)	0.99 (0.29, 3.35)	1.83 (0.48, 7.00)	1.09 (0.66, 1.80)	1.45 (0.26, 8.27)	2.32 (1.15, 4.69)[*]
Gay	2.80 (0.38, 20.56)	1.49 (0.48, 4.59)	1.54 (0.72, 3.32)	0.39 (0.19, 0.80)[*]	1.31 (0.31, 5.46)	0.93 (0.60, 1.45)	1.41 (0.18, 11.21)	0.69 (0.33, 1.45)
Bisexual	REF	REF	REF	REF	REF	REF	REF	REF
Born in France	0.60 (0.25, 1.46)	1.80 (0.72, 4.48)	1.56 (0.89, 2.76)	1.38 (0.56, 3.40)	0.76 (0.31, 1.86)	0.81 (0.58, 1.12)	0.42 (0.14, 1.23)	1.08 (0.55, 2.13)
Employment status								
Employed	REF	REF	REF	REF	REF	REF	REF	REF
Unemployed	1.80 (0.64, 5.04)	0.78 (0.32, 1.92)	0.60 (0.31, 1.18)	2.00 (0.98, 4.08)	0.83 (0.25, 2.76)	1.07 (0.72, 1.59)	0.94 (0.18, 4.93)	0.85 (0.37, 1.96)
Student	1.61 (0.43, 6.02)	0.89 (0.29, 2.68)	1.00 (0.49, 2.02)	0.69 (0.18, 2.71)	0.53 (0.12, 2.45)	0.84 (0.50, 1.40)	4.29 (0.72, 25.58)	1.91 (0.64, 5.74)
Current relationship status								
Single	REF	REF	REF	REF	REF	REF	REF	REF
Relationship with a man	0.51 (0.18, 1.48)	1.69 (0.95, 3.01)	0.86 (0.56, 1.31)	0.53 (0.22, 1.26)	1.37 (0.63, 2.98)	1.14 (0.85, 1.54)	0.90 (0.30, 2.66)	0.84 (0.48, 1.48)

^a Adjusted risk ratios (aRRs) with 95 % confidence intervals were calculated using log-binomial regression with covariates (age, sexual orientation, origin, employment and relationship status).

^b Due to the convergence problems with log-binomial model, a modified Poisson regression model with robust error variance was used.

* p<0.05;

** p<0.01

Table V

Mediation analyses^a of condomless anal intercourse and serosorting on popper use.

Independent variable	Mediating variable	Dependent variable ^b	NDE, Estimate (95% CI) ^c	NIE, Estimate (95% CI) ^c	MTE, Estimate (95% CI) ^c
Popper use	Condomless anal intercourse	PrEP candidacy	1.59 (1.14, 2.56)	1.14 (1.02, 1.36)	1.80 (1.30, 2.67)
	Serosorting	PrEP candidacy	1.50 (1.09, 2.16)	1.10 (1.00, 1.26)	1.65 (1.18, 2.39)

^aCovariates included age, sexual orientation, origin, employment and relationship status

^bUsed as dichotomous variable (Not sure/no vs. Yes)

^cBias-corrected 95% confidence intervals (CIs) were obtained using 1000 bootstrap samples.

NDE, Natural direct effect; NIE, natural indirect effect; MTE, marginal total effect