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Determining the roles that club drugs, marijuana, and heavy drinking play in PrEP medication adherence among gay and bisexual men: Implications for treatment and research

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Abstract

Researchers have established that substance use interferes with anti-retroviral medication adherence among gay and bisexual men (GBM) living with HIV. There is limited parallel examination of pre-exposure prophylaxis (PrEP) adherence among HIV-negative GBM. We conducted retrospective 30-day timeline follow-back interviews and prospective semi-weekly diary data for 10 weeks with 104 PrEP-using GBM, half of whom engaged in club drug use (ketamine, ecstasy, GHB, cocaine, or methamphetamine)—generating 9,532 days of data. Participants reported their day-by-day PrEP, club drug, marijuana, and heavy alcohol use (5+ drinks in one sitting). On average, club drug users were no more likely to miss a dose of PrEP than non-club drug users (M = 1.6 doses, SD = 3.0, past 30 days). However, we found that club drug use (at the event level) increased the odds of missing a dose on the same day by 55% and the next day (e.g., a "carryover effect") by 60%. Further, missing a dose on one day increased the odds of missing a dose the *following* day by eight-fold. We did not identify an event-level effect of marijuana use or heavy drinking on PrEP adherence. Our data suggest club drug users could have

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

greater protective effects from daily oral or long-acting injectable PrEP compared to a time-driven PrEP regimen because of the concurrence of club drug use and PrEP non-adherence.

RESUMEN

Los investigadores han establecido que el uso de sustancias interfiere con la adherencia a los medicamentos antiretrovirales entre los hombres gay y bisexuales (HGB) viviendo con el VIH. Hay limitada examinación en paralelo de la adherencia a la profilaxis pre-exposición (PrEP) entre los HGB VIH-negativos. Realizamos entrevistas retrospectivas de seguimiento histórico de 30-días y diarios prospectivos realizados dos veces a la semana por 10 semanas con 104 HGB que usan PrEP. La mitad de los participantes utilizaban drogas del club (ketamina, éxtasis, GHB, cocaína o metanfetamina)— generando 9,532 días de data. Los participantes reportaron uso diario de PrEP, drogas del club, marihuana y consumo excesivo de alcohol (5 o mas bebidas en una sesión). En promedio, los usuarios de drogas del club no tuvieron mas probabilidades de perder una dosis de PrEP que los usuarios que no usaban drogas del club (M = 1.6 dósis, SD = 3.0, pasados 30 días). No obstante, encontramos que el uso de drogas del club (al nivel de evento) incrementa la probabilidad de perder una dosis el mismo día por 55% y al próximo día (Por ejemplo, un “efecto de arrastre”) por 60%. Además, perder una dosis en un día aumenta ocho-veces la probabilidad de perder una dosis al día siguiente. No identificamos un efecto a nivel-evento entre uso de marihuana o alcohol excesivo y la adherencia a PrEP. Nuestra data sugiere que los usuarios de drogas del club pueden tener mayores efectos protectivos de PrEP diario oral, o PrEP de accion prolongada inyectable en comparación con un regimen de PrEP a nivel de tiempo debido a la concurrencia del uso de drogas del club y la falta de adherencia a PrEP.

Keywords

pre-exposure prophylaxis (PrEP); adherence; men who have sex with men; HIV; club drugs; alcohol; marijuana

INTRODUCTION

Nearly 70% of all new HIV infections in the United States (US) were among gay, bisexual, and other men who have sex with men (GBM) in 2016, and GBM accounted for 86% of incidence among adolescent and adult males.[1] In 2012, the US Food and Drug Administration (USFDA) approved a once-daily oral pill (Emtricitabine / Tenofovir) to prevent HIV called pre-exposure prophylaxis (PrEP).[2] PrEP was recommended for nearly 25% of GBM,[3] but newer estimates suggest as many as 64% of GBM would benefit from the protection PrEP offers.[4,5] In 2015, 9.1% of GBM identified as candidates for PrEP in a nationwide sample had a current PrEP prescription. PrEP uptake estimates among young GBM in major cities has ranged between 4.2% and 12.2% between 2013 and 2017, with highest uptake (i.e., 22.7%) specifically reported among young GBM who had partners living with HIV.[6–9] Although recent data indicate a 73% year-over-year increase in PrEP uptake from 2012–2016 in the U.S.,[10] fewer than 60,000 males (including men not identifying as GBM) were prescribed PrEP in mid-2017. The trajectory of increasing PrEP uptake could continue to rise as new dosing formulations (e.g., long-acting injectable PrEP) become available based on interest among GBM,[11–13] and alternative dosing may also help

increase PrEP persistence and adherence because many (i.e., 31–67%) daily oral PrEP users reported interest or willingness to switch to long-acting injectable PrEP.[14,15]

Compared to the general population, club drug use (i.e., ketamine, MDMA/ecstasy, GHB, cocaine, and methamphetamine) is more common among GBM.[16–28] GBM who use club drugs are at elevated risk for HIV transmission, especially those who combine substance use with sex. Researchers have consistently found a strong correlation between club drug use and condomless anal sex (CAS) in general, as well as concurrent CAS when having sex under the influence of club drugs.[28–38] Club drugs reduce inhibitions and make rational decision making difficult, which decrease the likelihood of engaging in protective behaviors such as condom use.[30,39] Substantial research also exists showing how club drugs negatively impact HIV medication adherence for GBM living with HIV.[19,40–49] Thus, club drug use presents a dual risk for HIV transmission—it decreases HIV medication adherence and increases the odds of CAS among GBM regardless of HIV-serostatus. For HIV-negative GBM who use club drugs, alternate strategies to protect against HIV transmission are warranted, such as the use of PrEP if their substance use does not impede adherence to support adequate protection against HIV.

Similar to club drugs, heavy alcohol use results in behavioral disinhibiting effects;[50] hazardous alcohol use has been associated with greater CAS among GBM[51] and lower HIV mediation adherence among samples of persons living with HIV including GBM,[52,53] particularly when used in combination with other drugs.[54,55] The study of hazardous alcohol use is especially important because of the deleterious effects on immune functioning caused by alcohol use,[56] which could increase the risk for HIV-seroconversion with inadequate PrEP adherence. One study of GBM in Atlanta found that 75% endorsed beliefs that alcohol had interactive toxicity effects with anti-retroviral medications; however, the study did not investigate if GBM purposefully missed PrEP doses timed around binge drinking events.[57] In contrast to alcohol and club drug use, recent evidence suggests no link between marijuana use and HIV medication non-adherence.[58,59] Nonetheless, further study is needed with PrEP users who use marijuana because of the varying contextual situations in which anti-retrovirals are used (i.e., for sustained health among people living with HIV compared to HIV prevention among PrEP users), which could result in differential adherence patterns.

HIV-negative GBM who use substances are likely to be ideal candidates for PrEP because of the well-documented association between substance use and CAS; however, their substance use might hinder adherence to PrEP based on literature supporting the role of substance use on HIV medication non-adherence among GBM. Substance use was identified as a barrier to PrEP use among 39.4% of stimulant (i.e., crack/cocaine and methamphetamine) users and 16.4% of alcohol users in prior research,[60] and HIV-negative GBM who used substances reported the deleterious effects of alcohol and club drugs (e.g., methamphetamine) on their PrEP adherence.[61] Despite the plausibility of substance use negatively affecting PrEP adherence, published evidence remains unclear. Stimulant users were more likely to have sub-optimal levels of Tenofovir drug concentrations compared to non-users in the iPrEx open-label extension study,[62] yet researchers associated with the PATH-PrEP cohort found differences in PrEP adherence among stimulant users by the number of CAS partners reported.[63] GBM who used stimulants and reported two or more partners had increasing

PrEP adherence over time, whereas GBM who used stimulants with zero or one CAS partner had decreasing PrEP adherence.[63] Further study of PrEP adherence among substance users, particularly with event-level data, is needed to describe and disentangle the potential causal relationship between substance use and PrEP adherence/non-adherence.

In this study, we recruited a sample of PrEP users to investigate the connection between substance use and PrEP adherence. By design, nearly half our participants were club drug users. Given the literature on ART adherence among GBM living with HIV and perceptions of HIV-negative substance users, we hypothesized substance use would be associated with declines in PrEP adherence with our event-level data from a New York City sample of GBM currently taking daily oral PrEP.

METHOD

Data for this manuscript were taken from *PrEP and Me,* a study of 104 GBM who were active PrEP users at the time of enrollment, as described previously.[14,64,65] Participants were recruited via targeted sampling,[66] which included advertising and preliminary screening for the study in gay concentrated neighborhoods and settings (e.g., gay bars, pride events, at LGBT community-based venues) as well as digital recruitment on gay hookup websites and apps, and social media. Those clicking one of our digital ads were routed to a secure online survey that assessed preliminary eligibility criteria. Those deemed preliminary eligible (in any screening setting) were asked to provide contact information for additional telephone-based screening with a member of our research team. Those eligible were scheduled for a face-to-face assessment at our research office.

To be eligible, participants had to 1) be 18 years or older, 2) cisgender male, 3) identify as gay or bisexual, 4) have been taking PrEP for at least 30 days, but not via a study that provided the PrEP medication (e.g., demonstration project, clinical trial), 5) reside in the New York City area, and 6) have access to the internet for completion of semi-weekly diary surveys. Our goal was to examine the role of club drug use on PrEP adherence, thus half of the sample were required to self-report club drug use in the 30 days prior to screening eligible. Club drugs included ketamine, MDMA/ecstasy, GHB, cocaine, or methamphetamine. All participants provided proof that they were taking PrEP by bringing their PrEP prescription bottle (along with their pills), with their name and date printed on it, to their study visit. Participants were compensated $40 for their baseline assessment as well as $4 for each of the twice-weekly diaries (see below) completed. All procedures were approved by the Institutional Review Board of the City University of New York.

Measures

Timeline follow-back interview.—As part of their baseline visit, participants completed a computer assisted survey as well as a structured 30-day timeline follow-back (TLFB)[67,68] interview (which retrospectively captured day-level substance use and PrEP adherence). The computerized survey included demographic measures such as age, race/ethnicity, educational attainment, income, relationship status, and length of time on PrEP.

The TLFB procedure reviews critical life events retrospectively to prompt recall of data, which were recorded into a personalized digital calendar. Interviewers were trained to use familiar language and vernacular of participants regarding drug names (e.g., meth, methamphetamine, tina, T, crystal). The TLFB has demonstrated good test-retest reliability, convergent validity, and agreement with collateral reports for drug use[69] and medication adherence.[70]

Online prospective diary.—Following their baseline assessment, participants completed prospective semi-weekly diary surveys for 10 weeks. For the prospective diary component, participants received an email at 8pm every Monday and Thursday containing a link to an online survey. Links themselves expired 24 hours after being sent. The online survey asked participants day-by-day about their PrEP adherence and substance use for the previous few days (i.e., on Thursdays, participants were asked about the preceding Tuesday and Wednesday, as well as that day (Thursday). On Mondays, participants were asked about the previous Friday, Saturday and Sunday, as well as that day (Monday)). Participants completed a twice-weekly diary as opposed to a daily diary to avoid pitfalls associated with the diary acting as a reminder to take their PrEP (an assessment effect).

The TLFB interview and prospective twice weekly diaries assessed for day-by-day use of club drugs (ketamine, ecstasy, GHB, cocaine, methamphetamine), marijuana, and heavy drinking (5 or more drinks in one sitting) as well as whether a PrEP dose was missed for each of the prior 30 days (for the TLFB) and prospectively for 10 weeks (via the twice weekly diary). TLFB interview data were extracted from digital calendars and imported into SPSS and merged with semi-weekly diary data for analysis.

Statistical Analyses

To capitalize on the extent of day-level data collected within this study from both the retrospective timeline follow-back interview and prospective diary, we created a combined day-level dataset with identical variables from both sources. To examine the impact of daily substance use on adherence to PrEP, we used a series of generalized linear mixed models conducted within SPSS 24 with days (i.e., level 1) nested within individuals (i.e., level 2). Across models, a dichotomous indicator of missing a PrEP dose (1 = missed dose, 0 = dose taken) was specified as the outcome using a binary distribution and logit link function.

At level 1, we included dichotomous indicators for daily club drug use (1 = yes), marijuana use (1 = yes), and heavy drinking (1 = yes) and adjusted for whether the collection of the data was on a weekend (1 = yes). Although prior research has shown similar effects when comparing data from TLFB and diary sources,[71,72] we nonetheless adjusted the model to assess the impact of whether data were collected via the TLFB or semi-weekly diary (1 = diary). At level 2, we adjusted for whether the individual was enrolled as a club drug user (1 = yes) as well as age, race (1 = White), education (1 = college degree or higher), and relationship status (1 = partnered). Across models, we used a random intercept as well as random slopes for all three of the level 1 substance use effects; we specified a variance components matrix for the random effects (i.e., we estimated only their variances and not their covariances). We modified the SPSS defaults to use Satterwhaite estimation of the

degrees of freedom, which is more conservative in estimating the significance of the level 2 effects, and robust estimation of the model standard errors.

In total, we ran three models: (1) a concurrent model, where the substance use and PrEP dosing occurred on the *same* day; (2) a time-lagged model where the PrEP dosing occurred on the next day after the substance use (i.e., a substance use "carryover effect" such to impact next day adherence); and (3) a time-lagged model where PrEP dosing occurred on the next day after substance use and we also adjusted, at level 1, for whether the *prior* day included a missed PrEP dose (1 = yes).

RESULTS

Table 1 reports demographic characteristics of the sample. Half (50.0%) of the GBM in this sample were men of color, most (71.2%) had a Bachelor's degree or more of education, and 42.3% made more than $50,000 annually in income. Mean age of sample was 32.5 years old. In total, 63.5% of men had been on PrEP for less than a year. Overall, men were highly adherent to their PrEP, missing an average of 1.6 doses (SD = 3.0) in the prior 30 days. By design, half (51%) of the men reported club drug use at the time of screening. Club drug users were significantly more likely to hold a Bachelor's degree and report an income over $50,000 a year. They did not differ by race or ethnicity, or length of time on PrEP.

We examined the retrospective TLFB data on drug use to further characterize between-person differences in use prior to the baseline—51.9% reported one or more day of use in the past 30 days. The most common drugs reported in the prior 30 days as captured within the TLFB were cocaine (34.6%), MDMA/ecstasy (26.9%), and GHB (16.4%); 13.5% of the sample reported methamphetamine use, and 11.5% ketamine. Meanwhile, although not criteria for enrollment, 54.8%% reported marijuana use and 71.2% reported heavy drinking in the prior 30 days. Club drug users were significantly more likely to report marijuana use and heavy drinking (see Table 1).

All analyses that follow are based on combined day-level data from both the TLFB interview and the subsequent 10-week diary. Across the 104 individuals in the sample, we analyzed 9,532 days of data for the concurrent models that focused on substance use and missed PrEP doses occurring simultaneously on the same day; due to loss of some data after matching contiguous days, 9,302 days of data were available for the time-lagged models focused on substance use predicting missed PrEP doses the *next* day.

The first model, in which we were looking at same-day effects of substance use on PrEP adherence, is displayed in Table 2. We found that club drug use was associated with significantly greater odds of missing a PrEP dose on that same day. Additionally, the model revealed that, at level 1, missing a PrEP dose was more likely on a weekend and, at level 2, that those with a college degree had lower odds of missing a PrEP dose on a typical day. The random variance for the intercept was significant, suggesting substantial between-person variability in the odds of missing PrEP on a typical day. We also found that the random variance for the day-level marijuana use slope was significant; in the presence of a non-significant slope, this suggests significant between-person variability in the impacts of

marijuana use on PrEP adherence and indicates there are likely level 2 (i.e., individual-level) factors that determine for whom marijuana use is associated with missing PrEP versus not.

The second model, in which we were looking at time-lagged effects of substance use on next-day PrEP adherence, is also displayed in Table 2. The findings from this second model were consistent with the first, showing a nearly identical, significant and positive effect of club drug use on missing a PrEP dose the *next* day. The main effect of whether the substance use occurred on a weekend was no longer significant when the outcome was no longer paired on the same day as the substance use; those with a college degree continued to have significantly lower odds of missing a PrEP dose on a given day. As with the prior model, there was significant random variability in the intercept and the slope for marijuana use.

The third model, in which we were replicating Model 2 while adjusting for whether there was a missed PrEP dose the day before, is not presented in tabular form. Consistent with the prior models, club drug use on the prior day remained a significant predictor as well (B = 0.35, Exp(B) = 1.42, p = 0.04, 95%CI[1.01, 1.98]), though missing a dose on the prior day was also significantly associated with missing a dose on the next day (B = 2.10, Exp(B) = 8.15, $p < 0.001$, 95%CI [4.76, 13.95]).

DISCUSSION

Researchers have established that substance use interferes with ART medication adherence among HIV-positive gay and bisexual men,[40–46,48,49,73–75] yet conflicting reports exist regarding the association between substance use and PrEP adherence among HIV-negative GBM.[62,63] In our study, club drug users—as a group—were no more likely to miss a PrEP dose than non-club drug users. However, instances of the *use* of club drugs at the event-level was significantly associated with missing a PrEP dose. In fact, this finding held true whether the impact of club drug use on PrEP adherence was modeled as missing a dose on the *same* day as the drug use as well as when modeled as missing a dose on the day *after* the drug use occurred. That is, although likelihood of taking PrEP on any given day was similar between club drug users and non-users, club drug use in-and-of-itself was significantly associated with missing a PrEP dose. These findings suggest that intervention strategies co-targeting club drug use and PrEP adherence may be warranted.

Our findings add to a growing body of research investigating substance use and PrEP adherence. In prior research, stimulant use at the aggregate level (i.e., using at least once in the past 30 days) was found to be associated with sub-optimal PrEP adherence in the iPrEx open label extension study.[62] However, when we considered a slightly broader category of club drug use, both in terms of a between-person differences (i.e., users vs. not) and within-person differences (i.e., specific events of use), we found only the latter was significantly associated with likelihood of missing a PrEP dose. Another group of researchers reported differences in PrEP adherence by stimulant use and number of sexual partners; over time, GBM who reported stimulant use—at the aggregate level—and multiple CAS partners had increasing PrEP adherence over time compared to stimulant users with fewer CAS partners (i.e., one or none).[63] In whole, our findings contribute to the effect stimulants and other club drugs have on PrEP non-adherence.

That being said, we recognize that adherence was high overall in the study—on average, participants missed fewer than two doses in the prior 30 days. Given the long half-life of Emtricitabine/Tenofovir,[76,77] participants in our study probably still had high protection from HIV infection in the event of a missed dose. In fact, studies have indicated that as few as four doses (out of seven) per week might be sufficient to provide protection from HIV.[78] Clinical trial researchers investigating alternate PrEP dosing schedules (i.e., on-demand, time-driven, and event-driven strategies)[79–81] found high levels of HIV protection even when PrEP is not taken every day. However, our findings do have implications for prescribing PrEP to club drug users. At the moment, once-daily PrEP is approved by the FDA. Were time-driven/event-based PrEP approved for use, adherence to scheduled doses would be critical. That is, our findings suggest that substance users might be better protected when prescribed daily dosing (whereby high levels of the drug are maintained even if an occasional dose is missed) as opposed to event-based dosing (whereby an individual has no/low PrEP in their system and additionally missed a critical dose because of their club drug use). Alternatively, club drug users might benefit from long-acting injectable PrEP—once available—by minimizing the harmful effects of their club drug use on their PrEP dosing because of the less frequent dosing requirements compared to oral PrEP.

In our study, heavy drinking was not associated with missing PrEP doses nor was marijuana use, *as day-level variables*. In models looking at both same-day missed doses as well as next-day missed doses, using marijuana and engaging in an episode of heavy drinking did not significantly impact PrEP use. However, we found that the random variance for the day-level marijuana use slope was significant. This indicates that there was significant between-person variability in the impact of marijuana on PrEP adherence, suggesting that there may be level 2 (i.e., individual-level) factors that moderate the impact of marijuana use on missing a PrEP dose. We also note that the overarching study was designed to assess for the role of club drug use on PrEP adherence, but also collected data on marijuana use and heavy drinking—finding null associations with PrEP adherence. Our null findings regarding heavy drinking at the day level conform with a prior report that found no association between heavy drinking and PrEP non-adherence at the aggregate level.[62]

We found that missing a PrEP dose on the prior day was associated with more than eight times the odds of missing a dose on the *next* day. This suggests there may be patterns (as opposed to randomness) in missing PrEP doses with a “carryover effect” to the next day. Multiple missed days of doses in a row can lower the plasma levels of Emtricitabine/Tenofovir beyond the protective threshold, as opposed to situations in which missing doses randomly throughout a week or month may not be as problematic depending upon their frequency. This too remains an area for further investigation with biological sampling, but further reduces our enthusiasm for on-demand PrEP dosing among club drug users.

Limitations

Our findings should be understood in the context of their limitations. First, the relatively modest sample size and recruitment of men only from New York City limits generalizability. Second, additional research is necessary to disentangle the specific substances (or combination of substances) that have the greatest impact on adherence, as well as why. Data

from persons living with HIV who engage in methamphetamine use have reported suboptimal adherence during episodes of drug “binges” that can last for several days.[40] Binge behavior has also been documented among users of other club drugs.[73,82] Qualitative data as well as quantitative data with a larger sample size would be useful in identifying the events leading up to and following missed doses.

Third, some of our data included TLFB interviews, which may be subject to recall and social desirability bias. Nevertheless, the TLFB interview procedure has been used in a variety of settings with GBM, particularly with regard to drug and alcohol use, ART adherence, and sexual behavior for recall periods spanning as far back at 6 weeks to 3 months, but it has yet to be validated for collecting data on PrEP adherence. Prospective twice weekly diaries can help to overcome some pitfalls of recall bias, but have the potential of reminding participants about their behavioral patterns (e.g., could serve as a PrEP medication reminder on the days in which the diaries are completed). Other methods of tracking adherence, such as prospective collection of dried blood spot samples or hair, could overcome some of the limitations of self-report.

Fourth, we note curious findings with regard to income differences between club drug users and non-users. In our sample, club drug users made greater incomes and this may be associated with the specific club drugs that appeared to be most common in this sample (cocaine and ecstasy). More in-depth examination of the role of socioeconomic status on PrEP adherence is warranted. Finally, we must highlight that we lack data on any motivations behind missing PrEP doses. It may be that missed doses were intentional or other factors—aside from club drug use—that predicated a missed dose (e.g., ran out of pills, have not had sex in a while). Anecdotally, because the TLFB is a qualitative interview, participants would have had the opportunity to explain why a dose was missed, but these did not evince themselves during data collection.

Conclusion

In our study, club drug users were no more likely to miss a dose than non-club drug users on average. However, we found that club drug use (at the event level) was associated with same-day missed doses as well as next day missed doses. Further, missing a dose on one day increased the odds of missing the dose the following day by eight-fold. Additional research is necessary to disentangle the mechanistic roles that club drugs play in non-adherence as well as to determine exactly which of the club drugs (and in what combinations) result in the greatest risk for missing a dose. Patterns of PrEP adherence in our data suggest club drug users could have greater protective effects from daily oral or long-acting injectable PrEP compared to a time-driven PrEP regimen because of the concurrence of club drug use and PrEP non-adherence. Finally, although we found that club drug was associated specifically with poorer PrEP adherence, we also highlight the need to investigate the role that substances may play other aspects of the PrEP care continuum,[83,84] as for example, they have been shown to impact the HIV treatment care continuum among populations of people living with HIV.[85]

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Table 1

Demographic and behavioral characteristics of PrEP-using gay and bisexual men, New York City

	Total sample		Non-users, *n* = 51		Club Drug[2] Users, *n* = 53			
Categorical Variables	***n***	***%***	***n***	***%***	***n***	***%***	χ^2	***p***
Race/Ethnicity								
Black	13	12.5	8	15.7	5	9.4	6.91	0.08
Latino	27	26.0	18	35.3	9	17.0		
White	52	50.0	21	41.2	31	58.5		
Other/Multiracial	12	11.5	4	7.8	8	15.1		
Race is non-White								
No	52	50.0	30	58.8	22	41.5	3.12	0.08
Yes	52	50.0	21	41.2	31	58.5		
Education								
Less than Bachelor's degree	30	28.9	20	39.2	10	18.9	5.24	0.02
Bachelor's degree or more	74	71.2	31	60.8	43	81.1		
Income								
Less than $50k per year	60	57.7	35	68.6	25	47.2	4.90	0.03
$50K or more per year Length of time on PrEP	44	42.3	16	31.4	28	52.8		
1–12 months	66	63.5	32	62.8	34	64.2	0.02	0.88
More than 1 year	38	36.5	19	37.3	19	35.9		
Missed any PrEP doses (past 90 days)								
No	41	39.4	20	39.2	21	39.6	0.00	0.97
Yes	63	60.6	31	60.8	32	60.4		
Marijuana Use (past 30 days)								
No	47	45.2	28	54.9	19	35.9	3.81	0.05
Yes	57	54.8	23	45.1	34	64.2		
Heavy Alcohol Use (past 30 days)[1]								
No	30	28.9	20	39.2	10	18.9	5.24	0.02
Yes	74	71.2	31	60.8	43	81.1		
Continuous Variables	*M*	*SD*	*M*	*SD*	*M*	*SD*	*OR*	*95% CI*
Age (range: 21–61 years old)	32.5	8.7	34.2	9.9	30.8	7.0	0.95	0.91–1.00

Note. M = mean; *SD* = standard deviation; *SE* = standard error; *OR* = odds ratio; *CI* = confidence interval

[1] five or more alcoholic drinks in one sitting

[2] self-reported use of ketamine, MDMA/ecstasy, GHB, cocaine, and/or methamphetamine in the past 30 days. Percentages may not add to 100 due to rounding.

Table 2.

Same-day and next-day associations between substance use and missed PrEP dosing.

	Model 1:[a] Same Day Missed PrEP			Model 2:[b] Next Day (Lagged) Missed PrEP		
	B	**Exp(B)**	**95%CI**	**B**	**Exp(B)**	**95%CI**
Fixed Components						
Level 1: Daily						
Intercept	−3.40	0.03***	[0.01, 0.08]	−3.28	0.04***	[0.02, 0.09]
Weekend (1 = yes)	0.38	1.46**	[1.16, 1.85]	0.11	1.12	[0.93, 1.34]
Collection method (1 = diary)	0.49	1.63	[0.91, 2.93]	0.50	1.64	[0.93, 2.90]
Club drug use (1 = yes)	0.44	1.55*	[1.01, 2.38]	0.47	1.60*	[1.06, 2.42]
Marijuana use (1 = yes)	0.29	1.34	[0.82, 2.18]	0.33	1.39	[0.85, 2.29]
Heavy drinking (1 = yes)	0.07	1.07	[0.82, 1.39]	0.07	1.07	[0.79, 1.45]
Level 2: Individuals						
Club drug user (1 = yes)	−0.01	0.99	[0.49, 2.00]	0.04	1.04	[0.53, 2.07]
Age	0.00	1.00	[0.95, 1.05]	0.00	1.00	[0.96, 1.05]
White race (1 = yes)	−0.01	0.99	[0.49, 2.00]	−0.04	0.96	[0.48, 1.93]
College degree (1 = yes)	−1.08	0.34**	[0.16, 0.74]	−1.12	0.33**	[0.15, 0.70]
Partnered (1 = yes)	0.40	1.50	[0.78, 2.87]	0.40	1.49	[0.78, 2.83]
Random Components						
Intercept variance	1.64**	--	[0.89, 3.05]	1.52**	--	[0.79, 2.96]
L1 Club drug use slope variance	0.19	--	[0.04, 0.90]	0.12	--	[0.01, 1.19]
L1 Marijuana use slope variance	0.77*	--	[0.35, 1.67]	0.80**	--	[0.38, 1.69]
L1 Heavy drinking slope variance	0.10	--	[0.02, 0.47]	0.16	--	[0.05, 0.55]

Note. N = 104

[a] N_{days} = 9,532

[b] N_{days} = 9,302.