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Journal

Journal of the International AIDS Society, 21(3)

ISSN

1758-2652

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Publication Date

2018-03-01



DOI

10.1002/jia2.25103

Peer reviewed

SHORT REPORT

Skating on thin ice: stimulant use and sub-optimal adherence to HIV pre-exposure prophylaxis

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Abstract

Introduction: Stimulant and heavy alcohol use are prevalent and associated with elevated risk for HIV seroconversion among men who have sex with men (MSM) and transgender women. In addition, each can pose difficulties for antiretroviral adherence among people living with HIV. Scant research has examined the associations of stimulant and heavy alcohol use with adherence to daily oral pre-exposure prophylaxis (PrEP) among MSM and transgender women. To address this gap in the literature, we evaluated the hypothesis that stimulant use and binge drinking are prospectively associated with sub-optimal PrEP adherence.

Methods: We analysed data from participants in a nested case-cohort in the iPrEx open label extension. Stimulant use (i.e. powder cocaine, crack-cocaine, cocaine paste, methamphetamine, cathinone) and binge drinking (i.e. ≥ 5 drinks in a single day) in the last 30 days were assessed. Baseline urine was tested for stimulants using immunoassays to reduce misclassification. Sub-optimal adherence was defined as tenofovir drug concentrations in dried blood spots less than 700 fmol per punch, indicative of less than four doses per week. We tested the prospective association of stimulant use and binge drinking with sub-optimal adherence at the 4-week follow-up visit.

Results and Discussion: Data from 330 participants were analysed. The majority of the participants were MSM (89%) with a median age at baseline of 29 years (interquartile range 24 to 39). Approximately 16% (52/330) used stimulants and 22% (72/330) reported binge drinking in the last 30 days. Stimulant users had fivefold greater odds of sub-optimal PrEP adherence compared to non-users in adjusted analysis (adjusted odds ratio [aOR] 5.04; [95% CI 1.35 to 18.78]). Self-reported binge drinking was not significantly associated with sub-optimal adherence after adjusting for stimulant use and baseline confounders (aOR 1.16 [0.49 to 2.73]). Depressive symptoms, being transgender, and number of sex partners were also not significantly associated with sub-optimal PrEP adherence ($p > 0.05$).

Conclusions: Stimulant use is a risk factor for sub-optimal PrEP adherence in the month following PrEP initiation. Comprehensive prevention approaches that reduce stimulant use may optimize PrEP adherence. Creating adherence plans that specifically address PrEP dosing in the context of ongoing stimulant use should also be considered.

Keywords: pre-exposure prophylaxis; adherence; drug use; stimulant use; binge drinking; men who have sex with men; transgender persons

Received 17 October 2017; Accepted 8 March 2018

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1 | INTRODUCTION

Men who have sex with men (MSM) are 24 times more likely to become infected with HIV compared to the general population, while transgender women are nearly 50 times more likely to become infected [1]. Daily oral HIV pre-exposure prophylaxis (PrEP) using emtricitabine-tenofovir disoproxil fumarate (FTC-TDF) has demonstrated efficacy in preventing HIV infection [2-6] and is a promising strategy for these key populations. In the iPrEx trial [2], MSM and transgender women taking PrEP had an overall 44% reduction in HIV acquisition. More recent data from the PROUD study [6] reported a

relative reduction of 86% among individuals taking daily oral PrEP, suggesting that this strategy is highly effective in preventing HIV in high priority populations.

However, the unprecedented clinical and public health benefits of PrEP require sustained, prevention effective levels of adherence during periods of exposure to HIV [3,7]. In the iPrEx Open Label Extension (OLE), drug concentrations in dried blood spots (DBS) corresponding to four or more doses of FTC-TDF per week (i.e. ≥ 700 fmol per punch) were associated with no new HIV infections [3]. But despite high interest and uptake of PrEP among MSM and transgender women [8,9], a considerable proportion of individuals either

discontinue or struggle to adhere to the regimen shortly after initiation [3,10]. In several studies, all acute HIV seroconversions occurred exclusively during periods of inadequate PrEP adherence or when PrEP was discontinued [3,4,7].

Existing studies have not clearly elucidated the reasons for sub-optimal PrEP adherence among MSM and transgender women [11], but alcohol and stimulant use may be important risk factors. Stimulant and heavy alcohol use are well-established correlates of HIV acquisition and poor treatment outcomes among HIV-positive individuals [12,13]. There is also increasing recognition that “chemsex,” or the use of a combination of sex enhancing drugs like stimulants, has become increasingly common among MSM residing in industrialized nations [14,15]. In a large observational study of MSM, stimulant use was independently associated with a threefold increase in risk for HIV seroconversion and an eightfold increase when combined with other chemsex drugs such as poppers [16]. In the United States, estimates of stimulant use range between 6% and 17% among MSM [17] and between 21% and 26% among transgender women [18-20]. Reports also suggest high rates of alcohol use in these individuals (approximately 56% in MSM and 44% in transgender women) [17,19]. However, the associations of stimulant use and heavy alcohol use with sub-optimal PrEP adherence is not well understood. To address this gap in knowledge, this study evaluated the hypothesis that stimulant use and binge drinking at baseline are prospectively associated with early sub-optimal PrEP adherence in an observational cohort of MSM and transgender women.

2 | METHODS

2.1 | Study participants

We analysed data from participants in a nested case-cohort in iPrEx OLE. Individuals in the case-cohort had drug concentrations measured at each time point after PrEP dispensation. The parent study and the design of the case-cohort are described in detail elsewhere [3,21]. Briefly, participants were enrolled at 11 sites across six countries (Brazil, Ecuador, Peru, South Africa, Thailand and the United States) between June 2011 and June 2012, and followed for up to 72 weeks. Visits were scheduled 4, 8 and 12 weeks after enrolment, and quarterly thereafter. Participants were male sex at birth, reported having anal sex with men, and were at least 18 years of age. All participants provided informed consent as part of the parent study. The iPrEx OLE study protocol was approved by institutional review boards at each site and by relevant national regulatory agencies. This study was approved by the Committee on Human Research at the University of California, San Francisco.

2.2 | Measures

2.2.1 | Stimulant use and binge drinking

Participants reported any stimulant use and binge drinking in the last 30 days using computer-assisted self-interview (CASI). Stimulants included powder cocaine, crack-cocaine, cocaine paste, methamphetamine, and the amphetamine analogue, cathinone. Immunochemical screening of banked urine collected at baseline was used to validate self-reported stimulant

use. Participants who denied any recent stimulant use but had a positive urine immunoassay were coded as having used stimulants. Binge drinking was defined as consuming ≥ 5 alcoholic drinks in a single day by self-report.

2.2.2 | Depressive symptoms

Depressive symptoms at baseline were measured using the Centre for Epidemiologic Studies Depression (CES-D) scale, a validated 20-item measure that assesses for the frequency of depressive symptoms in the past week [22]. Standard clinical cut-offs were used to categorize CES-D scores: none-mild depression (0 to 15); mild-moderate depression (16 to 26); and severe depression (≥ 27).

2.2.3 | Sexual risk behaviours

Condomless sex and the number of sex partners in the last three months were assessed at baseline using an interviewer-administered questionnaire.

2.2.4 | Sub-optimal PrEP adherence

Participants in the case-cohort had PrEP adherence estimated by tenofovir diphosphate (TFV-DP) concentrations in DBS, as described previously [3]. TFV-DP concentrations < 700 fmol per punch corresponds to an average of less than four doses per week. This dosing pattern provides sub-optimal protection against HIV [3].

2.3 | Analysis

We tested the direct association of baseline stimulant use and binge drinking with sub-optimal PrEP adherence at the 4-week follow-up visit using logistic models. Probability weights were used to account for the case-cohort design. As a sensitivity analysis, we repeated our analysis using a robust variance estimator to account for clustering within site. Because there were no observed differences in effect size estimates, we report analyses that do not adjust for clustering given the relatively modest number of sites in this project. We evaluated PrEP adherence at the 4-week follow-up visit based on previous analysis that demonstrated that poor adherence at this visit was highly predictive of future adherence patterns [23]. Relevant baseline confounders were identified using a directed acyclic graph [24]. Each predictor was modelled individually then as a predictor set. Covariate selection for the final model was based on changes in statistical precision [24]. Any sexually transmitted infection at enrolment was omitted in the final model as this resulted in a substantially larger standard error. Given the high prevalence of depression among MSM and transgender women [25,26] and the bivariate association between depression and non-adherence [27,28], we tested for the possible interaction between our predictors of interest and baseline CES-D score. We also tested for the possible interaction between stimulant use and binge drinking. However, we found no evidence of effect heterogeneity ($p > 0.05$) or any qualitatively meaningful changes in effect size estimates, so these terms were not included in the final model. All analyses were conducted using Stata 14 (College Station, TX).

3 | RESULTS

3.1 | Sample characteristics

A total of 349 participants were included in the iPrEx OLE case-cohort. Data from 330 participants who provided consent for long-term specimen banking and testing were included in this analysis (Table 1). Median age at baseline was 29 years (interquartile range [IQR] 24 to 39) and median number of sex partners in the last three months was two (IQR 1 to 5). Most identified as MSM (89%), Latino or Hispanic (57%), and had completed at least secondary education (78%). Approximately 16% (52/330) used stimulants and 22% (72/330) reported binge drinking in the last month. Nearly half (49%) of all participants reported engaging in any condomless sex in the previous three months at baseline.

3.2 | PrEP adherence

TFV-DP concentrations in DBS at the 4-week follow-up were available in 293 participants. Of those with available TFV-DP

Table 1. Baseline demographics and participant characteristics (N = 330)

	Median	(IQR)
Age	29	(24 to 39)
Total number of partners in last 3 months	2	(1 to 5)
	<i>n</i>	(%)
Study region		
Andes ^a	165	(50)
Brazil	68	(21)
South Africa	19	(6)
Thailand	18	(5)
United States	60	(18)
Men who have sex with men	295	(89)
Transgender women	35	(11)
Latino or Hispanic	187	(57)
Education		
Less than secondary	71	(22)
Completed secondary	106	(32)
Post-secondary	152	(46)
Baseline CES-D ^b score		
<16	237	(72)
16 to 26	63	(19)
≥27	29	(9)
Stimulant use in the last 30 days ^c	52	(16)
Binge in the last 30 days ^d	72	(22)
Condomless anal sex in the last 3 months	161	(49)

IQR, interquartile range.

^aIncludes sites in Ecuador and Peru.

^bCentre for Epidemiologic Studies Depression scale.

^cStimulant use based on self-report or positive urine immunoassay. Includes powder cocaine, crack-cocaine, cocaine paste, methamphetamine and cathinone (amphetamine analogue).

^d≥5 alcoholic drinks in a single day.

data, approximately 47% (137/293) had drug concentrations indicative of less than four doses in the prior week. Approximately 55% of stimulant users (24/44) and binge drinkers (34/62) were sub-optimally adherent at the 4-week follow-up visit.

In adjusted analysis, stimulant use was significantly associated with sub-optimal PrEP adherence (Table 2). Stimulant users were five times more likely to have TVF-DP concentrations <700 fmol per punch at the 4-week follow-up compared to non-users (adjusted odds ratio [aOR] 5.04; [95% CI: 1.35 to 18.78]). Binge drinking was not significantly associated with sub-optimal adherence (aOR 1.16 [0.49 to 2.73]). Total number of partners in the last three months and depressive symptoms were also not significantly associated with sub-optimal PrEP adherence. We found no statistically significant linear trend for total number of partners ($p = 0.87$) and CES-D score ($p = 0.79$) in the multivariable model. When we limited our analysis to only MSM, we observed a slightly larger association of stimulant use on sub-optimal adherence (aOR 8.82 [2.05 to 37.90]). The association of binge drinking remained non-significant (aOR 1.31 [0.52 to 3.34]).

4 | DISCUSSION

This study is among the first to document that stimulant use is associated with a fivefold greater odds of sub-optimal PrEP adherence, measured by TFV-DP drug concentrations below

Table 2. Baseline correlates of sub-optimal PrEP adherence at the 4-week follow-up visit (n = 293)

	Adjusted OR	(95% CI)	<i>p</i> -value
Stimulant use in the last 30 days ^a	5.04	(1.35 to 18.78)	0.02
Binge drinking in the last 30 days ^b	1.16	(0.49 to 2.73)	0.74
Transgender	1.24	(0.20 to 7.58)	0.82
Total number of partners in the last 3 months			
0 to 1 partners	Ref		
2 to 3 partners	0.78	(0.25 to 2.40)	0.67
≥4 partners	0.91	(0.28 to 2.99)	0.87
CES-D score ^c			
<16	Ref		
16 to 26	0.43	(0.15 to 1.18)	0.10
≥27	1.18	(0.34 to 4.11)	0.79

Multivariable model also controlled for study region, age, education, and Latino or Hispanic ethnicity. Sub-optimal adherence is defined as tenofovir diphosphate (TFV-DP) concentrations <700 fmol per punch based on dried blood spots (DBS), corresponding to <4 doses per week. All predictors were assessed at the baseline visit. We found no statistically significant linear trend for total number of partners ($p = 0.87$) and CES-D score ($p = 0.79$) in the multivariable model.

^aStimulant use based on self-report or positive urine immunoassay. Includes powder cocaine, crack-cocaine, cocaine paste, methamphetamine and cathinone (amphetamine analogue).

^bBinge drinking is ≥5 alcoholic drinks in a single day.

^cCentre for Epidemiologic Studies Depression (CES-D) scale.

the established threshold to maximize protection against HIV. The association between stimulant use and poor adherence to antiretroviral therapy is well-described in the HIV treatment literature [12,29,30], and findings from this study highlight that stimulant use may also undermine the clinical and public health benefits of PrEP.

PrEP implementation has slowly gained traction in recent years and data from real-world clinical experiences have shown encouraging results. Recent studies have reported high demand for PrEP in various clinical settings [31,32] and PrEP implementation outcomes have seen high overall rates of retention over time [33-35]. In a study examining retention in care outcomes in a community-based sexual health clinic in San Francisco, Hojilla et al. [35] found that stimulant use and unhealthy drinking behaviours were not significantly associated with PrEP discontinuation. However, an important limitation of the study was its limited ability to accurately measure PrEP adherence and recent drug and alcohol use. Because PrEP implementation is in its early stages [36-38], studies from clinical settings likely involve a large proportion of highly motivated early adopters that are not representative of the broader population of MSM and transgender women. Thus, important questions around potential barriers to optimal PrEP adherence in this key population remain unanswered. Although the field of PrEP research has advanced considerably since iPrEx OLE, data from this study remain particularly salient in the context of ongoing discussions around scale-up and developing strategies to optimize PrEP delivery with high priority populations.

Our findings support the need to provide PrEP as part of a comprehensive package that includes an assessment of potential barriers and interventions to enhance PrEP adherence. Buchbinder and colleagues' [39] secondary analysis of data from the randomized phase of iPrEx estimated that the lowest number needed to treat (NNT) occurred specifically among MSM and transgender women who used stimulants (NNT = 12). Thus, engaging stimulant users in the PrEP continuum is a high priority. Our work suggests that for PrEP to achieve its maximum clinical and public health impact, PrEP delivery models should incorporate efforts to optimize adherence in stimulant-using populations.

Focused work is needed to identify evidence-based interventions that can mitigate sub-optimal PrEP adherence in stimulant-using MSM and transgender women, particularly in the first month of starting the regimen. Expanded efforts with stimulant users could leverage intensive case management and follow-up to support PrEP adherence. Integration of evidence-based interventions that directly reduce stimulant use could also achieve meaningful improvements in PrEP adherence. For example, motivational interviewing and cognitive-behavioural interventions have demonstrated efficacy in reducing substance use and sexual risk taking in MSM [40,41]. Clinical research to develop and test interventions to optimize the prevention effectiveness of PrEP in stimulant users could achieve more meaningful reductions in HIV incidence.

This study has some limitations. Self-reported responses may have been prone to recall and social desirability biases, particularly for sensitive topics like alcohol and other substance use. We attempted to mitigate misclassification using urine biomarkers of stimulant use to validate participant responses, but this may have been incomplete based upon the limited window of detection for recent stimulant use. We

were also unable to differentiate between frequent and episodic stimulant and alcohol use, which may influence PrEP adherence in a dose-response manner. Binge drinking was operationalized as five or more alcoholic drinks in a single day rather than in one 2-hour sitting [42], which may have overestimated the number of individuals classified as binge drinkers in our study. As sexual risk can fluctuate over time [43], it is possible that some individuals only took PrEP during periods of possible exposure (e.g. on-demand dosing). Alternative dosing strategies might account for sub-optimal adherence in some participants. However, all individuals were counselled on the importance of daily PrEP use given the limited data available at the time on intermittent or on-demand PrEP use. Lastly, we acknowledge that transgender women are a distinct group of individuals that do not necessarily share the same psychosocial contexts as MSM. Our study was not sufficiently powered to detect differences between these groups. Future studies will need to examine transgender persons separately to clearly elucidate factors associated with PrEP adherence in this population.

5 | CONCLUSIONS

In this study, we utilized biomarkers of stimulant use to reduce misclassification and examined a validated biomarker of PrEP adherence as the outcome. Our findings demonstrate that stimulant use is a risk factor for sub-optimal PrEP adherence in the month following initiation. Identification of stimulant use as a risk factor for the impaired prevention effectiveness of PrEP is a crucial first step to inform the development of comprehensive approaches to optimize its clinical and public health benefits in high priority populations.

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COMPETING INTERESTS

DVG has received fees from Gilead Sciences. The other authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

A.C., K.R.M. and J.C.H. contributed to study concept and design. J.C.H., A.C., D.V., R.H., M.M., D.V.G. and R.M.G. contributed to data retrieval, analysis, or interpretation. J.C.H. and A.C. contributed to manuscript preparation. All authors provided critical review and edits. The final manuscript was approved by all authors.

ACKNOWLEDGEMENTS

The authors thank the iPrEx and iPrEx OLE participants, whose dedication to HIV research has made this work possible. We also thank Patricia Defechereux for her help in retrieving specimens from the iPrEx repository.

FUNDING

This study was supported by the National Institute on Drug Abuse (grant numbers R36 DA041906 and R01 DA033854). Funding support for iPrEx OLE (U01 AI064002) and for monitoring adherence using dried blood spots (U01

AI106499) was provided by the National Institute of Allergy and Infectious Diseases. Study medication for iPrEx OLE was donated by Gilead Sciences.

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