AIDS Care

Psychological and Socio-medical Aspects of AIDS/HIV

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/caic20

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To cite this article: Natalie M. Brousseau, Seth C. Kalichman, Ryan J. Watson & Lisa A. Eaton (2023): Amphetamine use and its associations with antiretroviral adherence and viral load among sexual minority men and transgender women living with HIV, AIDS Care, DOI: 10.1080/09540121.2023.2206096

To link to this article: https://doi.org/10.1080/09540121.2023.2206096

Published online: 03 May 2023.

AIDS CARE
https://doi.org/10.1080/09540121.2023.2206096

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Amphetamine use and its associations with antiretroviral adherence and viral load among sexual minority men and transgender women living with HIV

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ABSTRACT

Substance use has complex associations to HIV disease progression. The current study tested the associations between several substances and HIV viral load while accounting for confounders relevant to HIV disease progression and substance use. Young sexual minority men and transgender women living with HIV (LWH) in Georgia ($N = 385$) completed measures and biological tests for HIV viral load and substance use. Multivariable regression models tested the role of specific drugs (i.e., alcohol, cannabis/THC, cocaine, and combined amphetamine and methamphetamine) directly on viral load and indirectly through antiretroviral (ART) adherence. ART adherence and HIV care self-efficacy were consistently associated with greater HIV suppression. Alcohol and cocaine were not associated with ART adherence or viral load. Cannabis was negatively associated with ART adherence ($B = -.053$, $p = .037$) but not viral load. Amphetamine/methamphetamine demonstrated significant direct effects on higher viral load ($B = .708$, $p = .010$) while indirectly influencing viral load through a negative association with ART adherence. Our findings support previous research demonstrating amphetamine/methamphetamine use impacts viral load both directly and indirectly through ART adherence. Interventions addressing amphetamine/methamphetamine use by young sexual minority men and transgender women LWH are urgently needed, and future research should focus on determining the mechanisms by which formulations of amphetamine impact HIV replication.

Trial registration: ClinicalTrials.gov identifier: NCT03665532.

ARTICLE HISTORY
Received 18 July 2022
Accepted 17 April 2023

KEYWORDS
Amphetamines; HIV; ART adherence; viral load; substance use

Introduction

Substance use is a formidable barrier to the health of people living with HIV (PLWH), undermining HIV treatment and inhibiting progress throughout the HIV care continuum. Recreational and problematic patterns of substance use are highly prevalent among PLWH (Carrico, 2011; Kapadia et al., 2005). Substance use among PLWH is associated with increased HIV disease progression in part due to low antiretroviral therapy (ART) adherence which poses a serious risk to the health of PLWH and risks further HIV transmission to uninfected sex partners (Carrico, 2011; Kapadia et al., 2005). However, few studies have examined the impacts of specific substances, including alcohol and drugs, on ART adherence and HIV viral load, and the results of this research is mixed. One recent study examining alcohol use patterns and HIV disease progression demonstrated that when compared to abstinence, heavy drinking (i.e., >7 drinks/week for women or >14 drinks/week for men) was associated with unsuppressed HIV, whereas binge drinking (i.e., ≥4 or >5 drinks/occasion for women and men respectively) was not (Cook et al., 2017). Furthermore, mediation analyses suggest a small portion of the association between heavy drinking and suboptimal viral suppression was due to ART nonadherence. This supports similar studies that have found an association between alcohol use and HIV disease progression (Glynn et al., 2019). In contrast, other research has not found significant associations between alcohol use and viral load (Wu et al., 2011). Similar to alcohol use, multiple studies (Okafor et al., 2017) and a systematic review (Montgomery et al., 2019) have demonstrated mixed results for cannabis use and its association with viral load. However, research exploring alcohol and cannabis use has failed to account for potential confounders for both substance use and HIV treatment adherence such as access to HIV care, HIV care self-efficacy, prior substance use counselling (lifetime), and depressive symptoms.

Unlike other drugs, stimulant use (e.g., methamphetamine and amphetamines) among PLWH is emerging as a consistent risk factor for difficulties across the HIV care continuum. Studies suggests that those who use stimulants are less engaged in HIV care and more likely to report barriers to ART adherence, adversely

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impacting HIV viral load. A recent latent class analysis suggests people who use amphetamines and methamphetamines are less likely to be virally suppressed (Meyers-Pantele et al., 2021). Yet, despite these emerging patterns, it is unclear whether the association between stimulant use and viral load is accounted for by ART adherence. Furthermore, no recent study examining these effects has included the important confounding factors relevant to HIV and substance use.

The current study aimed to fill this gap in the literature by testing the direct and indirect effects of using alcohol, cannabis, cocaine, amphetamine, and methamphetamine use on viral load. This study is first known to assess these effects among young sexual minority men and transgender women from the US South, while also controlling for potential confounders relevant to both substance use and HIV treatment.

Methods

Participants and setting

The sample included 385 individuals assigned male at birth, with 47 participants identifying as transgender. Participants were recruited through clinical, community and social media outlets between September 2017 and December 2019. Eligible participants were between the ages of 18 and 36 years old, and all participants were asked to provide documentation of HIV positive status. The study was conducted in the Atlanta metro area of Georgia, US which has an annual HIV incidence of 28 per 100,000 population, the highest rate of HIV among all US states (CDC, 2019; Sullivan et al., 2020).

Procedures

Young adults living with HIV were recruited to take part in a treatment engagement and ART adherence study (registered clinicaltrials.gov NCT03665532). PLWH were recruited through targeted ads and flyers available within the community including partnering infectious disease clinics and social media. Sampling included adapted participant-driven snowball-sampling techniques, where participants were encouraged to refer other PLWH and compensated $25. A video-chat procedure was used to screen potential participants, during which they were asked to confirm their age and HIV status with a photo ID and proof of HIV positive status (e.g., antiretroviral medication prescription, lab results).

Following informed consent, participants completed demographic and health measures via computer assisted self-interviews (CASI), provided blood samples for viral load testing, and urine samples for bioanalysis including alcohol, cannabis, cocaine, amphetamine, and methamphetamine. ART adherence was also assessed via two unannounced phone-based pill counts following the initial interview. All participants received behavioural counselling to assist HIV care engagement and adherence. Participants were reimbursed with up to $193 for completing all measures and providing biological specimens. Participant privacy was protected through a federal certificate of confidentiality and the University of Connecticut Institutional Review Board approved all study procedures.

Measures

Computerised interviews

Demographic and health characteristics. Participants were asked their age, gender identity, race/ethnicity, and income. Income was measured ordinally: (1) $0–$10,000; (2) $11,000–$20,000; (3) $21,000–$30,000; (4) $31,000–$40,000; (5) $41,000–$50,000; (6) $51,000–$60,000; (7) $61,000 or higher. *Substance use counselling* was measured dichotomously with one question asking if the participant had ever received substance use counselling. The Centers for Epidemiological Studies Depression scale (CESD) was used to assess symptoms of depression (Radloff, 1977). Twenty items assessed the frequency of participants' thoughts, feelings and behaviours in the past week, with responses *0 = 0 days, 1 = 1–2 days, 2 = 3–4 days, 3 = 5–7 days*. Scores were summed, ranging from 0 to 60 where values greater than 16 met the subthreshold for depressive symptoms, Cronbach's α = .91.

HIV care self-efficacy. Based on theories of health behaviour change (Bandura, 2005), HIV care self-efficacy was adapted from the HIV Medication Taking Self-Efficacy Scale judging a participant's confidence that they could adhere to HIV care under various circumstances (Erlen et al., 2010). Five questions assessed: (1) How certain are you that you can follow all of your HIV doctor's orders?; (2) How certain are you that you can keep your next HIV doctor appointment?; (3) How certain are you that you can take your HIV medications if you're having side effects?; (4) How certain are you that you can take your HIV medications around other people?; (5) How certain are you that you can take your HIV medications if away from home? Responses ranged from 0 ("*not at all certain*") to 10 ("*very certain*") and the final score was averaged. A higher score indicates better HIV care self-efficacy, Cronbach's α = .88.

Access to HIV care. Four items assessed participants' access to HIV care, adapted to reflect significant barriers to HIV care including participants' ability to pay for

transportation, HIV care costs, culturally based stigma, and an inability to understand medical instructions (Mgbere et al., 2015). Responses ranged on a five-point ascending confidence scale from 0 ("*very hard*") to 4 ("*very easy*") where the final scores were averaged. Higher scores signified fewer barriers or greater access to HIV care, Cronbach's α = .83.

Substance use biomarkers

Alcohol use. We used a point-of-care urine dip test for Ethyl glucuronide (EtG), a minor non-oxidative hepatic metabolite of ethanol used to index recent alcohol use (Wurst et al., 2005). Urine EtG tests have shown 50% sensitivity for detecting alcohol use in 24 h, 100% sensitivity for alcohol use in 12 h (Andresen-Streichert et al., 2018) and can detect alcohol use for up to five days depending on the amount of alcohol consumed (Lowe et al., 2015).

Drug use. We assessed drug use with a 12-panel urine dip-test conducted onsite with participant consent. This test strip uses a lateral flow chromatographic immunoassay for qualitative detection of 12 drugs/metabolites, including cannabis (THC), cocaine, amphetamine, and methamphetamine (Redwood Toxicology Labs – Redi-test-12). These tests are FDA approved and are reliable and valid for detecting recent use (72–96 h). In addition to alcohol use, cannabis, cocaine, amphetamines, and methamphetamines demonstrated the highest frequencies of use. Based on previous research (Meyers-Pantele et al., 2021) and exploratory univariate results (see data analyses), amphetamines and methamphetamines were combined into a single dichotomous index entitled amphetamine use.

ART adherence

Antiretroviral therapy adherence was assessed via two unannounced phone-based ART pill counts over 30 days. Upon completing their initial interview, participants were informed about the pill count procedure and were trained in the process necessary to complete a pill count via phone (e.g., gathering all ART medications from around the house and other spaces). Over the next 30 days, participants were called twice. While these phone calls were not scheduled, participants were asked which days/times would be most convenient. The first phone call was used to establish the base number of ART pills in the participant's possession. The second phone call was used to count the number of remaining pills. Both pill counts were then used to calculate a ratio of ART pills counted to prescribed, considering the initial number of pills dispensed, the number of pills taken daily, the amount of time between the unannounced phone calls, and the number of pills remaining (Kalichman et al., 2008). The unannounced pill count procedure has been deemed as both a reliable and valid method to assess ART medication adherence via phone (Bangsberg, 2001).

HIV viral load

To determine HIV RNA plasma concentrations (viral load) participants provided 80 µL of fingerstick blood for dried blood spots collected in Hemaspot HF devices. HIV-1 viral load testing was conducted using the Abbott *RealTime* HIV-1 assay, a reverse transcription-PCR assay performed on the automated Abbott *m*2000 platform (Abbott Molecular Inc., Des Plaines, IL). The limit of detection of the assay is 2.92 log (831 copies/mL), a threshold that nearly eliminates most errors caused by viral load blips or assay variability (Crepaz et al., 2016). Raw viral load results were then log-transformed for interpretability.

Data analyses

SPSS version 28 was used for all analyses. The demographic characteristics of the sample were partitioned by amphetamine/methamphetamine use (vs. no use) to allow for comparisons between the primary groups. Difference testing was then used to explore the targeted sociodemographic factors. Specifically, t-tests tested the mean differences for continuous sociodemographic variables (e.g., age by amphetamine use) and χ^2 tests were used to assess the differences in categorical sociodemographic variables (e.g., transgender status by amphetamine use). Multicollinearity was not an issue as no independent variables were correlated at .80 or greater. Based on previous research (Meyers-Pantele et al., 2021) and univariate results, amphetamine use and methamphetamine use were combined into a single dichotomous index entitled amphetamine use. Specifically, both amphetamine and methamphetamine had significant direct associations with ART adherence (AMP $B = -.108$, $p = .024$; M-AMP $B = -.127$, $p = .018$) and viral load (AMP $B = .019$, $p = .008$; M-AMP $B = .022$, $p = .010$). Further, 72% of participants ($n = 49$) who tested positive for amphetamines also tested for methamphetamines, suggesting a high frequency of co-use. Thus, amphetamine and methamphetamine use were combined into a single index labelled amphetamines. Using the guidelines of Preacher and Hayes, SPSS PROCESS was used for mediation analyses (Hayes, 2012). Multivariable linear regression models tested the role of specific drugs (i.e.,

Table 1. Demographic and health characteristics of young sexual minority men and transgender women living with HIV.

	Amphetamine use ($n = 68$)	No amphetamine use ($n = 317$)		
	Mean (*SD*) /*n* (%)		*t*	X^2
Viral Load	1.89 (2.09)	0.89 (1.63)	−3.37***	–
Adherence	0.65 (0.26)	0.75 (0.25)	2.43	–
Age	29.73 (3.66)	28.99 (3.83)	−1.38	–
Income	1.97 (1.19)	2.55 (1.59)	2.59***	–
Depressive symptoms	24.17 (13.09)	18.67 (12.13)	−3.20	–
HIV Self-efficacy	8.53 (1.88)	8.80 (1.51)	1.22	–
Access to HIV care	2.40 (1.05)	2.70 (1.04)	1.76	–
Substance use counsel	17 (25.0%)	75 (23.7%)	–	5.07*
Transgender	6 (8.8%)	29 (9.1%)	–	0.19
Race/Ethnicity				
Black	65 (95.6%)	280 (88.3%)	–	0.15
Hispanic/Latino	3 (4.4%)	37 (11.7%)		
Positive Biomarker Test				
Alcohol	14 (20.6%)	99 (31.2%)	–	0.24
Cannabis/THC	46 (67.6%)	242 (76.3%)	–	6.77**
Cocaine	19 (27.9%)	46 (14.5%)	–	19.50***

Note. $N = 385$. Income is represented ordinally: (1) $0–$10,000; (2) $11,000–$20,000; (3) $21,000–$30,000; (4) $31,000–$40,000; (5) $41,000–$50,000; (6) $51,000–$60,000; (7) $61,000 or higher. Positive biomarker tests represent *n* (%) participants testing positive for alcohol and drug use via urinalysis. Amphetamine use is a combined index reflecting amphetamine and methamphetamine use. * $p \leq 0.05$; ** $p \leq 0.01$; ***$p \leq 0.001$.

alcohol, cannabis, cocaine, and amphetamines) directly on HIV viral load and indirectly through their effects on ART adherence while controlling for key demographic (i.e., age, income, transgender status, and race/ethnicity) and health characteristics (i.e., HIV care self-efficacy, access to HIV care, substance use counselling, and depressive symptoms).

Results

Among the 385 sexual minority men and transgender women LWH, 90% were Black with an average age of 29. Within the full sample, the most common drug used was cannabis (75%) followed by alcohol (29%), cocaine (17%), methamphetamines (14%), and amphetamines (12%). Participant demographics were further partitioned based on a positive or negative urinalyses for amphetamine use (Table 1). Participants who used amphetamines had significantly higher viral loads, more substance use counselling, more cocaine use, lower income, and lower cannabis use compared to those who did not test positive for amphetamines.

Multivariable models

Multivariable mediation analyses were conducted using ordinary least squares path analysis to assess each substance's direct effect on viral load and indirect effect through ART adherence controlling for key demographics, depressive symptoms, HIV care self-efficacy, access to HIV care, and history of substance use counselling.

Alcohol use

Alcohol was measured via the presence of EtG. The full model was not significant. For the direct effects, high ART adherence was negatively related to a lower viral load ($B = -.753$, $p = .011$). Among the covariates, those reporting greater HIV care self-efficacy ($B = -.150$, $p = .021$) had lower viral loads. Further effects were not significant, suggesting alcohol was not associated with ART adherence and HIV viral load (Table 2).

Cannabis use

The full model was significant for cannabis ($r^2 = .053$, $F(10, 374) = 2.099$, $p = .024$). More cannabis use was negatively related to ART adherence ($B = -.053$, $p = .037$), and low ART adherence was associated with a higher viral load ($B = -.781$, $p = .010$). Among the covariates, those reporting greater HIV care self-efficacy ($B = -.138$, $p = .031$) had lower viral loads. Further effects were not significant, suggesting cannabis use may have a detrimental impact on ART adherence but not viral load (Table 3).

Cocaine use

When assessing cocaine use, the full model was significant ($r^2 = .057$, $F(10, 374) = 2.250$, $p = .014$). High ART adherence was associated with lower viral load ($B = -.799$, $p = .016$). Participants with greater HIV care self-efficacy ($B = -.135$, $p = .034$) and no history of substance use counselling ($B = .389$, $p = .044$) had lower viral loads. Further effects were not significant, suggesting cocaine use was not associated with ART adherence and viral load (Table 4).

Amphetamine use

The model for amphetamine use was significant ($r^2 = .070$, $F(10, 374) = 2.788$, $p = .001$), and all the direct effects were significant (Table 5). More amphetamine use (*a* path) was negatively associated with lower ART adherence ($B =$

Table 3. Multivariable regression results for alcohol predicting viral load.

	B	*B SE*	95% CI *LL*	95% CI *UL*	*p*
Direct effects					
Cannabis use→ART Adherence (a) *	**−.053**	**.027**	**−.105**	**−.013**	**.037**
ART Adherence→Viral Load (b) **	**−.781**	**.334**	**−1.437**	**−.125**	**.010**
Cannabis use→Viral Load (c′)	−.099	.173	−.439	.242	.570
Covariates					
Age	−.023	.022	−.066	.020	.233
Race/Ethnicity	.126	.233	−.446	.471	.789
Income	−.021	.059	−.137	.095	.711
Depressive symptoms	−.002	.008	−.017	.013	.814
Transgender	.135	.302	−.459	.728	.655
HIV care self-efficacy *	**−.138**	**.064**	**−.263**	**−.015**	**.031**
Access to HIV care	−.039	.093	−.144	.222	.670
Substance use counsel	.397	.247	−.089	.884	.100
	B	Boot *SE*	Boot 95% CI *LL*	Boot 95% CI *UL*	
Indirect effect					
Cannabis use→ART Adherence→Viral Load	.041	.030	−.004	.114	

Note: $N = 385$. 95% CI = confidence interval; LL = lower limit; UL = upper limit. (*a*), (*b*), and (*c*′) label mediation pathways. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ (significant effects bolded).

Table 4. Multivariable regression results for cocaine predicting viral load.

	B	*B SE*	95% CI *LL*	95% CI *UL*	*p*
Direct effects					
Cocaine use→ART adherence (*a*)	−.065	.040	−.144	.014	.100
Adherence→Viral Load (*b*) *	**−.799**	**.333**	**−1.453**	**−.145**	**.016**
Cocaine use→Viral Load (*c*′)	−.343	.259	−.851	.166	.186
Covariates					
Age	−.023	.022	−.066	.020	.288
Race/Ethnicity	−.006	.233	−.464	.452	.971
Income	−.027	.059	−.143	.089	.650
Depressive symptoms	−.002	.008	−.017	.013	.766
Transgender	.136	.301	−.455	.728	.651
HIV care self-efficacy *	**−.135**	**.064**	**−.260**	**−.019**	**.034**
Access to HIV care	−.048	.093	−.135	.230	.609
Substance use counsel *	**.389**	**.246**	**.044**	**.095**	**.873**
	B	Boot *SE*	Boot 95% CI *LL*	Boot 95% CI *UL*	
Indirect effect					
Cocaine use→ART Adherence→Viral Load	.052	.042	−.018	.146	

Note: $N = 385$. 95% CI = confidence interval; LL = lower limit; UL = upper limit. (*a*), (*b*), and (*c*′) label mediation pathways. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ (significant effects bolded).

−.103, $p = .010$). Low adherence was associated with higher viral load (*b* path) ($B = -.662$, $p = .032$), and more amphetamine use was associated with higher viral load (*c* path) ($B = .708$, $p = .010$). Likewise, greater HIV care self-efficacy was associated with lower viral load ($B = -.148$, $p = .019$). The model also showed that amphetamine use indirectly influenced HIV viral load through its effects on ART adherence ($B = .079$, 95% CI: 0.061–0.210).

Discussion

The current study tested the direct effect of using alcohol, cannabis, cocaine, and amphetamine on HIV viral load and each substances' indirect effect via ART adherence while controlling for key demographic and health characteristics. As expected, higher ART adherence and greater HIV care self-efficacy were consistently associated with lower HIV viral load. Alcohol and cocaine use were not associated with ART adherence or HIV viral load. Cannabis use was negatively associated with ART adherence but not viral load. Among all substances tested, only amphetamine use demonstrated both a direct association with viral load and an indirect association through ART adherence.

Our findings demonstrate that amphetamine use is associated with HIV viral load over and above ART adherence. Further, amphetamine use had indirect effects on viral load through ART adherence. These results bolster similar findings between stimulant use and viral load (Carrico et al., 2014), including previous studies that indicate amphetamine use has an independent impact on HIV replication (Carrico et al., 2014).

Table 5. Multivariable regression results for amphetamines predicting viral load.

	B	*B SE*	95% CI *LL*	95% CI *UL*	*p*
Direct effects					
Amphetamine use→ART adherence (*a*) **	**−.103**	**.044**	**−.189**	**−.017**	**.010**
ART adherence→Viral Load (*b*) *	**−.662**	**.332**	**−1.314**	**−.100**	**.032**
Amphetamine use→Viral Load (*c'*) **	**.708**	**.284**	**.151**	**1.265**	**.010**
Covariates					
Age	−.030	.022	−.073	.013	.107
Race/Ethnicity	.209	.231	−.434	.476	.928
Income	−.001	.058	−.116	.114	.771
Depressive symptoms	−.003	.008	−.018	.015	.600
Transgender	.182	.299	−.408	.771	.540
HIV care self−efficacy *	**−.148**	**.063**	**−.273**	**−.024**	**.019**
Access to HIV care	−.034	.092	−.146	.215	.708
Substance use counsel	.390	.245	−.090	.871	.111
	B	Boot *SE*	Boot 95% CI *LL*	Boot 95% CI *UL*	
Indirect effect					
Amphetamine use→ART Adherence→Viral Load	**.079**	**.054**	**.061**	**.210**	

Note: $N = 385$. 95% CI = confidence interval; LL = lower limit; UL = upper limit. (*a*), (*b*), and (*c'*) label mediation pathways. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ (significant effects bolded).

Likewise, results align with a recent study where PLWH with elevated amphetamine use were 3.5 times more likely to have a detectable viral load 5-months later compared to those low in substance use (Meyers-Pantele et al., 2021). Further, when comparing across multiple substances, Meyers-Pantele et al. (2021) found that the elevated alcohol, THC, and cocaine use class did not impact later viral load when accounting for amphetamine use. While more research is needed across alcohol and drugs, these findings point to the future importance of accounting for polydrug use and/or co-use and how the combinations of certain substances may exacerbate behaviours and symptoms relevant to PLWH.

The current findings should be considered in light of limitations. First, while multiple substances were tested, our sample size prevented controlling for and simultaneously testing use of multiple substances within the same model. Our analyses are essentially correlational and cannot infer directionality. While exploratory univariate results supported a combined index of amphetamine and methamphetamine use, there may be certain distinct differences between these two drug classes that are not represented. Further research into multiple formulations of amphetamines among PLWH should consider these differences and test whether the effects of other drug use on viral load remain significant when controlling for amphetamine use. Likewise, it may be important for future research to use a combination of biomarkers and/or self-report testing to triangulate substance use patterns. For example, the current study explored alcohol use via EtG testing. While EtG testing has its strengths, there are also inherent weakness in capturing alcohol use within a finite period. Triangulation or some combination of self-report and biomarkers may provide a better picture of consistent substance use patterns to determine problematic periods of substance use over time.

In conclusion, the current findings expand our knowledge on the impacts of specific drug use on critical HIV outcomes including ART adherence and viral load. These results suggest amphetamine use may play a uniquely important role in HIV treatment by impacting HIV replication both directly and indirectly through ART adherence. It may be important for HIV care providers to assess initial amphetamine and methamphetamine co-use in their patients, especially interventions aimed at decreasing amphetamine use among PLWH have achieved durable and clinically meaningful reductions to HIV viral load (Carrico et al., 2019). Further, future interventions targeting young PLWH who actively use substances should be tailored to specify the substances use in the context of HIV care. For example, while reducing alcohol and cannabis use may aim to improve ART adherence to suppress HIV, abstinence from amphetamine use may be necessary for optimal viral suppression.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by National Institute on Drug Abuse [grant numbers R01-DA033067 LAE; K01-DA047918 RJW].

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