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Authors

Fulcher, Jennifer A
Javanbakht, Marjan
Shover, Chelsea L
et al.

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COMPARATIVE IMPACT OF METHAMPHETAMINE AND OTHER DRUG USE ON VIRAL SUPPRESSION AMONG SEXUAL MINORITY MEN ON ART

Jennifer A. Fulcher[a,b], **Marjan Javanbakht**[c], **Chelsea L. Shover**[c], **Amy Ragsdale**[c], **Ron Brookmeyer**[d], **Steven Shoptaw**[e], **Pamina M. Gorbach**[a,c]

[a]Division of Infectious Diseases, Department of Medicine, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave, Los Angeles, CA, 90095, USA.

[b]VA Greater Los Angeles Healthcare System, 11301 Wilshire Blvd, Los Angeles, CA, 90095, USA.

[c]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, 650 Charles E Young Dr S, Los Angeles, CA, 90095, USA.

[d]Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles, 650 Charles E Young Dr S, Los Angeles, CA, 90095, USA.

[e]Department of Family Medicine, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave, Los Angeles, CA, 90095, USA.

Abstract

Background: Substance use decreases the likelihood of achieving undetectable HIV viremia; however, the comparative effects by drug have not been fully described. In this study, we compare the effects of methamphetamine use versus other drugs on viremia in sexual minority men on antiretroviral therapy (ART).

Methods: HIV-positive participants currently on ART (N=230) were selected from an ongoing cohort of diverse young sexual minority men (mSTUDY) enrolled from August 2014 to May 2018. Substance use and sociodemographic factors associated with viremia outcomes were assessed using ordinal regression analysis with generalized estimating equations. Viremia outcomes were grouped as undetectable (≤20 copies/ml), low level suppressed (21–200 copies/ml), or not suppressed (>200 copies/ml).

Corresponding Author: Jennifer Fulcher, MD, PhD, 10833 Le Conte Ave, CHS 37-121, Los Angeles, CA 90095, P: (310) 825-7225, F: (310) 825-3632, jfulcher@mednet.ucla.edu.

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Author Disclosures

Conflict of Interest No conflict declared.

Results: The prevalence of drug use across 825 study visits was 73%, with methamphetamine use most prevalent (50%). After adjusting for unstable housing and ART adherence, methamphetamine use, either alone (adjusted OR=1.87; 95% CI 1.03–3.40) or with other drugs (adjusted OR=1.82; 95% CI 1.12–2.95), was associated with higher odds of increasing viremia compared to no drug use. Other drug use excluding methamphetamine did not show a similar association (adjusted OR=1.29; 95% CI 0.80–2.09). Among our study population, nearly half the instances of viremia could be reduced if methamphetamine was discontinued (attributable fraction=46%; 95% CI 3–71%).

Conclusions: Methamphetamine use, either alone or in combination with other drugs, is associated with failure of viral suppression among sexual minority men on ART independent of adherence and sociodemographic factors. This accounts for nearly half of the observed instances of unsuppressed viremia in this study.

Keywords

HIV-1 infection; methamphetamine; men who have sex with men; antiretroviral therapy

1. INTRODUCTION

Substance misuse is an ongoing public health issue with myriad adverse health effects. Among people living with HIV (PLWH), substance misuse contributes to disease progression and, ultimately, increased mortality(Adams et al., 2018; Kapadia et al., 2005). A recent multi-site substance use prevalence study found that among PLWH, substance use disorder was more prevalent in men who report sex with men (53%) than those who did not (41%)(Hartzler et al., 2017), which is consistent with prior studies(Mimiaga et al., 2013). Stimulant use, including methamphetamine, is particularly prevalent among sexual minority men living with HIV(Colfax and Shoptaw, 2005; Mimiaga et al., 2013). Methamphetamine has detrimental effects on disease progression(Carrico et al., 2014), and retention in HIV care(Horvath et al., 2013), even in the era of universal treatment(Carrico et al., 2019).

It is known that substance use decreases the odds of viral suppression(Carrico et al., 2019; Ellis et al., 2003; Fairbairn et al., 2011; Feldman et al., 2015), and the comparative effects by drug have only recently been examined(Liang et al., 2020; Nance et al., 2020). Much of the negative effects of drug use on viral suppression are attributed to decreased access to therapy and antiretroviral therapy (ART) adherence(Horvath et al., 2013; Palepu et al., 2011). However, some studies have suggested that certain stimulant drugs, such as methamphetamine, reduce viral suppression even in the presence of ART(Carrico et al., 2019; Ellis et al., 2003; Liang et al., 2020) and coordinated medical care(Li et al., 2020).

Viral suppression (HIV RNA <200 copies/ml) improves clinical outcomes and reduces HIV morbidity and mortality(Bernal et al., 2018). However, some studies of low level viremia (HIV RNA 20–200 copies/ml) have shown increased virological failure compared to persons with undetectable virus(Laprise et al., 2013; Vandenhende et al., 2015). The effects of drug use on low level viremia compared to undetectable is not known.

This study sought to compare the effects of methamphetamine and other polysubstance use on levels of viremia in a cohort of HIV-infected sexual minority men on ART. We hypothesized that compared to visits with no drug use, visits reporting any drug use would be associated with increased viremia, and that methamphetamine use specifically would be associated with greater viremia.

2. METHODS

2.1 Study participants

Participants were selected from an ongoing cohort examining substance use and HIV in young sexual minority men (mSTUDY, NIDA U01 DA036267). The mSTUDY was approved by the UCLA Office of the Human Research Protection Program Institutional Review Board (IRB) and all subjects provided written informed consent at study entry. Data used in this study were collected from August 2014 to May 2018. Participants were eligible for the mSTUDY if they: (1) are between 18 and 45 years of age, (2) identified as male at birth, (3) reported sex with men, (4) capable of providing informed consent, and (5) willing and able to return to the study every six months to complete study related activities. By design, half of the participants were HIV-positive and half were HIV-negative. Inclusion criteria for this analysis was HIV-positive and on ART based on clinician review of concurrent medications and self-report. All mSTUDY participants complete biannual visits consisting of medical history, clinical examination, laboratory tests (including plasma HIV RNA quantification), urine drug screening, specimen collection for biorepository, and detailed behavioral questionnaire. Substance use data over the preceding six months was collected using computer-assisted self-interview. Drugs queried included: methamphetamine, ecstasy, cocaine, heroin, cannabis, prescription drugs, other party drugs (GHB, LSD, ketamine). Response options for frequency of use included: never, once, less often, monthly, weekly, daily.

2.2 Statistical analysis

Viremia outcomes (plasma HIV RNA quantification results) were grouped into three categories: undetectable (≤ 20 copies/ml), low level suppressed (21–200 copies/ml), or not suppressed (>200 copies/ml). Descriptive statistics were calculated for total visits and by viremia group. Factors associated with viremia group (i.e. our outcome/dependent variable) were assessed using regression analysis with generalized estimating equations (GEE) in order to account for the within subject correlations. We fit models with random intercepts and time effects to accommodate the repeated measures gathered from each participant and to allow participant-specific changes in the responses over time (i.e. time-varying covariates). Variables tested for inclusion in the multivariable models were based on univariate analyses or specified *a priori* as risk factors based on the existing literature, and included sociodemographics (age, race/ethnicity, unstable housing), clinical characteristics (duration of HIV-infection, ART adherence, and missed appointments), and substance using behaviors (i.e. exposure/independent variable). In order to estimate the specific contribution of methamphetamine use with viremia, the attributable fraction (AF) was calculated such that $AF = Ie - Iu / Ie = RR - 1 / RR$ where Ie is the incidence of viremia among methamphetamine users, Iu is the incidence of viremia among non-methamphetamine users,

and RR represents the relative risk of viremia by substance use group. All statistical analysis was performed using SAS version 9.4 (SAS Inc., Cary, NC).

3. RESULTS

3.1 Characteristics of the study population.

This study included 230 HIV-positive sexual minority men in Los Angeles, CA with an average age of 34 years (range 18 – 45). The majority race/ethnicity groups were Hispanic (37.2%) and non-Hispanic Black (38.3%). A large proportion of participants were unemployed (59%), and 34.6% had experienced homelessness in the past six months. The majority of unemployed and/or homeless participants reported methamphetamine or other substance use in the past six months (Table 1).

All participants had chronic HIV infection, only 5.7% were diagnosed within the past year, and all were prescribed ART. The median HIV RNA was 20 copies/mL (IQR <20 – 280) and CD4+ T lymphocytes was 571 (IQR 359 – 794). Participants reported missing at least one dose of ART in the past week at 49% of visits. For the purposes of this study, we grouped HIV RNA copies into undetectable (≤ 20 copies/ml), low level suppressed (21–200 copies/ml), or not suppressed (>200 copies/ml). The rationale for this grouping is that among persons with detectable viremia, those who maintain suppressed viral loads may have less risk of mortality or virologic failure(Bernal et al., 2018; Laprise et al., 2013; Vandenhende et al., 2015). Therefore, we felt it was important to differentiate between low level suppressed and not suppressed viremia.

3.2 Substance use prevalence and characteristics.

A total of 826 study visits were included in this analysis. There was an average of 2 visits (1–7 range) per participant with a mean duration of follow-up 1.4 years (95% CI 1.2–1.5). The prevalence of self-reported drug use in the past six months across study visits was 73%, with the majority of participants reporting methamphetamine use (50%). Frequency of methamphetamine use was weekly or daily at 52% of visits with methamphetamine use. The next most prevalent drug was cannabis, reported at 46% of all study visits with substance use. Among visits with reported methamphetamine use, 22% of these visits included polysubstance use with other drugs, most commonly cannabis. Other stimulant use (cocaine) was reported at 15% of study visits with substance use. Opioid use was reported at only a minority of visits (2%) with substance use. Due to low number of visits with reported use for some substances, all drugs other than methamphetamine were grouped together for further analysis.

3.3 Association between substance use and viremia.

Participants had suppressed viremia (HIV RNA <200 copies/ml) at the majority of visits (76%), including undetectable virus at 61% of visits. Adjusting for repeated observations, there were significant differences in unstable housing, reported missed ART doses, and missed appointments with HIV care provider among viremia categories (Table 2). Unsurprisingly, those with uncontrolled viremia (HIV RNA >200 copies/ml) were more likely to have experienced unstable housing, have missed at least one ART dose in the past

week, and missed at least one appointment with HIV care provider in the past six months. When examining distribution of substance use among viremia categories, only methamphetamine use was significantly different with a greater proportion in the HIV RNA >200 copies/ml group. Among those visits with self-reported daily or weekly methamphetamine use, 44.4% (88/194) had uncontrolled viremia (HIV RNA >200 copies/ml) compared to only 15.4% (64/415) of visits with no self-reported methamphetamine use.

We next used ordinal logistic regression to examine factors associated with increasing HIV viremia (Table 2). Both unstable housing (Adjusted OR 1.34, 95% CI 0.92–1.96) and missing at least one ART dose (Adjusted OR 2.12, 95% CI 1.54–2.91) were associated with greater odds of viremia, therefore these covariates were included in the subsequent analysis to account for the effects of adherence and housing on the relationship between drug use and viral suppression. Since methamphetamine use was the only drug significantly different among viremia categories, we specifically examined the odds of viremia among methamphetamine users. Substance use other than methamphetamine did not significantly increase odds of viremia (Adjusted OR 1.29, 95% CI 0.80–2.09). Methamphetamine use, either alone (Adjusted OR 1.87, 95% CI 1.03–3.40) or with other drugs (Adjusted OR 1.82, 95% CI 1.12–2.95), was associated with nearly two-fold greater odds of viremia compared to non-users. Among this study population, nearly half the cases of viremia could be reduced if methamphetamine use was discontinued (attributable fraction=46%; 95% CI 3%−71%).

4. DISCUSSION

In this study we examined comparative effects of methamphetamine and other drug use on HIV viremia among sexual minority men on ART. We found that men who use methamphetamine, either alone or with other drugs, have nearly two-fold increased odds of unsuppressed viremia. This same risk was not seen with other drug use. Similar to prior studies(Hinkin et al., 2007; Horvath et al., 2013; Jin et al., 2018; Parsons et al., 2013), we also found that decreased ART adherence and decreased adherence to HIV care were more prevalent among methamphetamine users, and these factors certainly contribute to failed viral suppression. However, our analysis also found increased odds of viremia among methamphetamine users even after controlling for ART adherence. At least one other study has found similar findings(Ellis et al., 2003). While there are certainly additional unaccounted behavioral factors, these findings also raise the possibility of a contributing biological mechanism. *In vitro* and *in vivo* mouse studies have shown that methamphetamine can directly activate virus production among infected cells(Toussi et al., 2009), which may contribute to persistent viremia in the presence of ART. Several translational studies have also identified immune alterations in methamphetamine users that could contribute to viral replication and persistence(Carrico et al., 2018; Grosgebauer et al., 2019; Massanella et al., 2015). Additionally, it is possible that methamphetamine may interact with some antiretroviral drugs to alter metabolism through the cytochrome P450 system(Dostalek et al., 2007). Such an interaction has been suggested between nicotine and certain protease inhibitors(Higgins et al., 2007). Identifying these mechanisms will be important to improve outcomes and decrease transmission among methamphetamine users living with HIV.

Strengths of this study include the robust size with multiple visits over time, a racially and ethnically diverse population, and the ability to comparatively examine the effects of methamphetamine versus other drug use on viremia. This is among the first studies to examine different drugs in PLWH on ART. Nance et al found that abstinence in drug use increased odds of viral suppression for opioids, methamphetamine, cocaine, and cannabis; importantly, even reduction in drug use increased odds of viral suppression for opioids and methamphetamine(Nance et al., 2020). Liang et al showed that crack cocaine, but not other drugs, was associated with increased viral load(Liang et al., 2020). Our study similarly found a significant impact of methamphetamine on viral suppression but did not find similar associations with other substances, likely due to limited power to examine these other drugs in our cohort. Notably, similar to Liang et al, we restricted our study to participants on ART and included an assessment of recent ART adherence in our models, to look for effects of drug use beyond ART access and adherence.

Limitations of this study include the use of data from a single cohort. Though ethnically diverse, all participants were from similar geographic locations and only included sexual minority men. As ART may potentially have different metabolism and efficacy in women(Gandhi et al., 2004), understanding the effects of substance use on viral suppression in women on ART is an important area for future investigation. In this analysis, we used substance use and ART adherence data collected via self-report only. Self-reports of illicit behaviors such as substance use are subject to reporting bias(Fendrich et al., 1999), but use of self-administered survey strategies (e.g. computer-assisted self-interview) help to significantly reduce this bias. Additionally, the time frame of self-reported ART adherence is shorter than substance use in this study, which limits our ability to fully account for ART adherence in our analyses. Though we attempted to include other social characteristics that may affect viral suppression in our analysis, such as homelessness, we cannot exclude the possibility of other confounders.

4.1 Conclusions

Addressing substance use is an important focus to improve clinical outcomes among PLWH. In this study we showed that methamphetamine use in particular may account for up to 40% of instances of unsuppressed viremia in sexual minority men on ART. While achieving viral suppression is the goal to improve clinical outcomes among PLWH, it is also important for reducing HIV transmission. In the era of treatment as prevention and U=U(Fauci et al., 2019), interventions that target factors that increase the likelihood of viral suppression are important for preventing new HIV infections. Focused efforts on reducing substance use, particularly methamphetamine use, is an important component in the goal of ending the HIV epidemic.

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Highlights

- Methamphetamine use is associated with poor HIV control among sexual minority men on antiretroviral therapy
- Relationship between methamphetamine use and poor HIV control remains even after accounting for medication adherence and sociodemographic factors
- Other substance use does not have the same association with poor HIV control in this study population
- Nearly half of the instances of uncontrolled HIV could be eliminated by stopping methamphetamine use in this study population

Table 1.

Baseline characteristics among HIV+ sexual minority men on ART, by drug use status

	Total (n=230)		Drug Use, past 6 months						
			Meth use (n=132)		Other drug use (no meth) (n=56)		No drug use (n=42)		p-value[b]
	n	%[a]	n	%	n	%	n	%	
Socio-demographic characteristics									
Age in yrs, mean (SD)	34.0 (6.4)		34.1 (6.0)		32.8 (7.3)		35.0 (6.0)		0.21
Race/ethnicity									0.52
African American	88	38.3	45	34.1	28	50.0	15	35.7	
Hispanic/Latino	86	37.2	52	39.4	16	42.9	18	42.9	
Other	17	7.4	11	8.3	4	4.8	2	4.8	
White	39	16.9	24	18.2	8	16.7	7	16.7	
Education									0.93
< High School	36	15.9	23	17.7	7	12.5	6	15.0	
High School Graduate	86	38.1	49	37.7	22	39.3	15	37.5	
> High School	104	46.0	58	44.6	27	48.2	19	47.5	
Unemployed	131	59.0	86	67.7	28	51.2	16	40.0	<0.01
Unstable Housing, past 6 months[c]	80	34.6	63	47.7	12	21.4	5	6.3	<0.01
Ever incarcerated	105	45.6	74	56.1	16	28.6	15	35.7	<0.01
HIV characteristics									
HIV diagnosis <1 year ago	13	5.7	5	3.8	7	12.7	1	2.4	0.30
Missed >1 ART dose, past 7 days	113	49.0	74	56.1	20	35.7	19	45.2	0.07
HIV RNA (copies/ml), median (IQR)	20 (<20–280)		20 (<20–2,390)		20 (<20–160)		20 (<20–60)		0.16
CD4+ T lymphocytes (cells/ml), median (IQR)	571 (359–794)		578 (309–840)		551 (265–677)		583 (384–734)		0.99

Abbreviations: meth, methamphetamine; SD, standard deviation; IQR, interquartile range; ART, antiretroviral therapy

Sum may not equal total due to missing information

[a] Percentages refer to column percentages

[b] p-values calculated using chi-square test, t-test, and Kruskal-Wallis test as appropriate

[c] Defined as not having a regular place to stay in the past 6 months

Table 2.

Prevalence and correlates of HIV viremia among HIV+ sexual minority men on antiretroviral therapy using ordinal logistic regression

	HIV RNA copies/mL (at time of visit)							Outcome Viremia			
	≤20 copies/mL (n=505 visits)		21 – 200 copies/mL (n=126 visits)		≥ 200 copies/mL (n=195 visits)		p-value[a]	Unadjusted OR	95% (CI)[a]	Adjusted OR	95% (CI)[a]
Socio-demographic characteristics											
Age at study visit, mean (SD)	34.8 (6.6)	34.0 (6.6)	35.9 (6.1)	0.38	1.01	(0.98–1.04)	--	--			
Race/ethnicity							0.35				
African American	174	56.1	48	15.5	88	28.4		1.57	(0.89–2.77)	--	--
Hispanic/Latino	203	62.6	52	16.1	69	21.3		1.16	(0.71–1.91)	--	--
Other	41	66.1	10	16.1	11	17.7		0.98	0.48–2.16)	--	--
White	87	66.9	16	12.3	27	20.8	1.00	Reference	--	--	
Unstable Housing, past 6 months[b]							<.01				
Yes	102	51.5	34	17.2	62	31.3		1.69	(1.17–2.43)	1.34	(0.92–1.96)
No	403	64.2	92	14.7	133	21.2	1.00	Reference	1.00	Reference	
HIV related factors											
HIV diagnosis < 1 year ago							0.08				
Yes	7	36.8	7	36.8	5	26.3		1.91	(0.91–3.99)	--	--
No	483	61.8	113	14.5	185	23.7	1.00	Reference	--	--	
Missed at least 1-dose of ARTs, past 7 days							<.01				
Yes	224	52.3	61	14.3	143	33.4		2.43	(1.76–3.36)	2.12	(1.54–2.91)
No	281	70.6	65	16.3	52	13.1	1.00	Reference	1.00	Reference	
Missed at least 1-appointment with HIV care provider, past 6 months							<.01				
Yes	156	47.7	57	17.4	114	34.9		2.74	(1.99–3.80)	--	--
No	318	70.7	64	14.2	68	15.1		1.00	Reference	--	--
Substance use behaviors											
Smoker, current (cigarettes)							0.02				
Yes	147	53.3	45	16.3	84	30.4	1.62	(1.07–2.45)	--	--	
No	283	64.5	65	14.8	91	20.7		1.00	Reference	--	--
Binge drinking, past 6 months							0.94				

	HIV RNA copies/mL (at time of visit)							Outcome Viremia			
	≤20 copies/mL (n=505 visits)		21 – 200 copies/mL (n=126 visits)		≥ 200 copies/mL (n=195 visits)		p-value[a]	Unadjusted OR	95% (CI)[a]	Adjusted OR	95% (CI)[a]
Yes	212	61.5	52	15.1	81	23.5	0.99	(0.68–1.42)			
No	293	61.0	74	15.4	113	23.5		1.00	Reference	--	--
Drug use (mutually exclusive categories), past 6 months											
Methamphetamine only	172	53.6	47	14.6	102	31.8	<.01	2.31	(1.27–4.22)	1.87	(1.03–3.40)
Methamphetamine (and other drugs)	49	55.1	12	13.5	28	31.5		2.41	(1.48–3.94)	1.82	(1.12–2.95)
Other drug use (excluding methamphetamine)	126	64.6	32	16.4	37	19.0		1.42	(0.86–2.35)	1.29	(0.80–2.09)
No drug use	158	71.8	35	15.9	27	12.3		1.00	Reference	1.00	Reference

Abbreviations. ART=Antiretroviral Therapy; SD=Standard Deviation; OR=Odds ratio

[a] p value adjusts for the effect of the subject (i.e. multiple observations for the same participant)

[b] Defined as not having a regular place to stay in the past 6 months