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Longitudinal patterns of illicit drug use, antiretroviral therapy exposure and plasma HIV-1 RNA viral load among HIV-positive people who use illicit drugs

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Abstract

Objectives: HIV-positive people who use illicit drugs (PWUD) experience elevated rates of HIV-associated morbidity and mortality compared with members of other key affected populations. Although suboptimal levels of access and adherence to antiretroviral therapy (ART) are common among HIV-positive PWUD, there is a need for studies investigating the possible biological impacts of noninjection illicit drug use among people living with HIV in real-world settings.

Methods: We accessed data from the ACCESS study, an ongoing prospective cohort of illicit drug users with systematic HIV viral load monitoring in a setting with universal care and ART dispensation records. We used multivariable generalized linear mixed models to estimate the longitudinal associations between noninjection use of crack cocaine, powder cocaine, opioids, methamphetamine, cannabis and alcohol on plasma HIV-1 RNA viral load, adjusted for ART exposure and relevant confounders.

Results: Between 2005 and 2018, 843 individuals from the ACCESS cohort were included and contributed to 8698 interviews. At baseline, the mean age was 43 years, 566 (67%) reported male sex and 659 (78%) used crack cocaine in the previous 6 months. In multivariable models adjusted for ART exposure, only crack cocaine use in the last 6 months was found to be significantly associated with higher HIV viral load.

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Conflicts of interest

There are no conflicts of interest.

Conclusion: We observed significantly higher HIV viral load during periods of crack cocaine use independent of ART exposure. Our findings support further research to investigate the possible biological mechanisms of this effect.

Keywords

antiretroviral therapy; crack cocaine; disease progression; drug use disorders; highly active; HIV-1

INTRODUCTION

People who use drugs (PWUD) typically experience higher rates of HIV acquisition, more rapid HIV disease progression and greater rates of HIV-associated morbidity and mortality than members of other key affected populations [1–3]. Elevated rates of HIV transmission and HIV-associated morbidity and mortality are due, in part, to lower levels of optimal access and adherence to ART observed among HIV-positive PWUD [4–6].

Despite the many behavioural, social/structural and economic barriers to optimal HIV treatment engagement faced by PWUD [4,7], the impact of substance use on HIV disease progression is not completely understood. A wealth of clinical studies have detailed how psychoactive substance use, via links to poorer rates of access and adherence to ART, indirectly contribute to swifter HIV disease progression [8–10]. At the same time, some observational studies have identified potential direct biological links between psychoactive substance use and HIV disease progression, possibly via modulation of the host immune system and increased viral replication [11–15]. For example, a study of 222 HIV-positive people who use illicit drugs found that crack cocaine use during the study period was significantly associated with 2.14 swifter rates of progression to $CD4^+$ cell count 200 cells/μl and higher HIV viral load, after adjustment for self-report adherence to ART [16].

Unfortunately, the existing evidence base is limited by a number of methodological weaknesses: Cross-sectional studies have limited ability to assess the impact of substance use on HIV disease progression; longitudinal studies to date typically rely on participant self-report of adherence to ART. In addition, although most studies have focused on injection drug use (IDU), there is a need to better understand the effect of noninjection drug use, including stimulant use, and alcohol use [2,17]. Accordingly, the objective of this study was to assess the impact of specific types and frequencies of noninjection substance use on HIV disease, specifically plasma HIV-1 RNA viral load, independent of ART exposure. This evaluation was performed using data from an open prospective cohort of PWUD recruited from community settings in a jurisdiction with universal no-cost access to HIV care and treatment.

MATERIALS AND METHODS

Study population

Data for this analysis were collected from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing prospective observational cohort of PWUD. The ACCESS cohort and recruitment process has been described in detail previously [18,19]. The

ACCESS cohort recruits HIV-positive individuals who are aged 18 years or older, use illicit drugs (e.g. heroin, methamphetamine and crack cocaine) other than or in addition to cannabis in the previous month (which was illegal during the study period), and provided written informed consent. Study participants were recruited from the Downtown Eastside neighbourhood of Vancouver, Canada through extensive street outreach. This area has a high prevalence of substance use, HIV infection, marginalization and criminalization [20]. ACCESS participants completed an interviewer-administered questionnaire that collected baseline and bi-annual information on a range of exposures and outcomes, including lifetime and recent substance use behaviours (including route of administration and frequency), sociodemographic characteristics, health service utilization and interactions with the criminal justice system. Clinical examination and blood draws were completed by a study nurse to determine $CD4^+$ cell counts and HIV-1 RNA plasma viral load. Complete retrospective and prospective HIV profiles for individuals are produced by confidentially linking the research data collected to clinical and ART dispensation records in the Drug Treatment Programme (DTP) at the BC Centre for Excellence in HIV/AIDS, the province-wide ART dispensary and HIV clinical monitoring registry. Specifically, the DTP processes all prescriptions written by physicians for antiretroviral therapy and dispenses the medication to a predesignated access point (e.g. hospital, community-based pharmacy, correctional facility and so on) for pick-up. ART is typically provided in 30-day increments and only medication dispensed and picked up is included in the DTP dataset. Participant data are confidentially linked using their personal health number (PHN), a unique and persistent 10-digit identifier issued to all residents of the province of British Columbia.

Participants in the ACCESS cohort receive $30 (CAD) honorarium for each study visit. The ACCESS study was approved by the Providence Healthcare/University of British Columbia Research Ethics Board.

For the present analysis, the study sample was restricted to participants who completed more than one study interview between 1 December 2005 and 30 April 2018. Only observations from individuals with at least 1 $CD4^+$ and at least 1 HIV viral load observation within 180 days of their earliest interviews were included.

Measures

The primary outcome of interest was HIV-1 RNA plasma viral load (log10[copies/ml]). We used the mean of all observations in the last 6 months or, if none, we used the most recent observation.

The primary explanatory variables were time-updated frequency measures of substance use in the last 6 months aggregated into three-levels (i.e. none, any, at least daily). The substances were alcohol, cannabis, noninjection crack cocaine, noninjection powder cocaine, noninjection opioids (i.e. both illicit and prescribed opioids) and noninjection methamphetamine. We also considered secondary variables hypothesized to be associated with either the outcome or explanatory variables, including age (per year older), sex at birth (male vs. female), homelessness (yes vs. no), IDU (yes vs. no) and $CD4^+$ cell count (at baseline). All variables except sex and $CD4^+$ cell count were time-varying and referred to the 6-month period prior to each study interview (or, for age, the date of the study interview.)

To account for the possible impact of substance use on engagement and adherence to ART (i.e. the indirect effect of substance use on HIV viral load), we also included a measure of exposure to ART using data from the DTP, the local province-wide HIV treatment registry. Specifically, at each study interview, we calculated the number of days in the previous 180 days for which ART had been dispensed and picked up, whether in community, clinical or carceral settings. Notably, this treatment was not directly observed. All time-varying variables refer to the 6-month period prior to the follow-up interview.

Statistical analyses

First, we determined the baseline characteristics of the primary and secondary variables of the study population stratified by their noninjection drug-use patterns. We then built six models using generalized-linear mixed-effects models (GLMM), one for each of the primary explanatory variables. Each of the six models included the bivariate and multivariable (confounding) relationships. The confounding multivariable GLMM represented relationship between the outcome variable and the main explanatory variable while adjusting for other secondary confounding variables; secondary variables were removed in a stepwise manner if they did not produce at least 5% change in the relationship between the outcome variable and the drug use explanatory variable. Data were analysed using R (version 3.5.0; R Foundation for Statistical Computing, Vienna, Austria), and all P values are two-sided.

RESULTS

Between December 2005 and April 2018, 945 individuals were recruited and, after applying the inclusion criteria, 843 (89%) were included in these analyses. A comparison of excluded (102, 11%) and included participants at baseline is presented in Supplementary Table 1, http://links.lww.com/QAD/B732. Notably, included participants did not differ from excluded by median HIV viral load [3.1 vs. 4.0 $\log_{10}$(copies/ml), $P = 0.273$] nor by patterns of recent substance use except cannabis (57 vs. 43% in the last 6 months, $P = 0.008$.) Included participants were more likely to be male, older, with lower $CD4^+$ cell counts and more days of ART exposure in the previous 6 months at baseline (all $P < 0.05$). In total, the 843 included participants contributed 8698 interviews during the study period.

The baseline characteristics of the study population are presented in Table 1, and the observed events during the entire study period are presented in Table 2. At baseline, 659 (78%) reported using crack cocaine and 481 (57%) reported using cannabis in the last 6 months. People using methamphetamine had the youngest median age (41 years) compared with the median age of the entire study population (43 years). At baseline, the median baseline HIV viral load was 3.1 [interquartile range (IQR) = 1.7–4.5] $\log_{10}$ copies/ml and median HIV viral load of all observed interviews (including follow-up visits) was 1.6 (IQR = 1.5–3.3) $\log_{10}$ copies/ml. The baseline median $CD4^+$ cell count was 340 (IQR = 210–500) cells/μl and median ART exposure was 179 (IQR = 117–180) days. For all interview periods, the median $CD4^+$ cell count was 375 (IQR = 240–547) cells/μl and median ART exposure was 180 (IQR: 143–180) days. Polysubstance use was common: On average, participants reported using 2 (IQR = 1–3) substances over all study interviews. Most

interviews (5210, 60%) contained a report of at least two substances used in the last 6 months.

In the multivariable analyses presented in Table 3, any (vs. none) crack cocaine use was positively associated with HIV viral load [β = 0.068, 95% confidence interval (95% CI): 0.022–0.113]; at least daily (vs. none) crack cocaine use was positively associated with HIV viral load (β = 0.163, 95% CI: 0.104–0.221). No other substance was significantly associated with an HIV viral load in multivariable analyses.

DISCUSSION

In this study, we observed a significant association between crack cocaine use and increased HIV viral load that was independent of our measure of ART exposure. Compared with periods of no crack cocaine use, frequency of crack cocaine use (none vs. any vs. at least daily in the last six months) was linked to higher HIV viral load in a dose-dependent fashion.

Previous longitudinal studies investigating the impact of noninjection stimulant use on HIV disease progression in the era of combination ART have produced mixed findings but were also marked by important methodological limitations [16,17,21–25]. In studies of progression to AIDS and death [21–23,25], stimulant use was not associated with mortality among 1313 MSM in the Multicenter AIDS Cohort study [21]. However, in two studies from the Women's Interagency HIV Study [22,23], persistent crack cocaine use was linked to triple the risk of death after adjustment for self-reported ART adherence [22]; similarly, both stimulant and poly-drug use were associated with swifter rates of progression to AIDS after controlling for ever being exposed to ART [23]. Our findings are consistent with two longitudinal studies that assessed the link between stimulant use and HIV viral load [16,17]. In a clinic-based study of 1635 HIV-positive individuals on ART [17], cumulative stimulant use (defined as any methamphetamine or powder cocaine use, crack cocaine use or powder cocaine injection) was linked in a dose-dependent fashion to HIV viral load nonsuppression. Similarly, crack cocaine use was associated with higher HIV viral load among 222 HIV-positive individuals in a model adjusted for self-reported ART adherence (β = 0.325, P = 0.029) [16]. Our study builds on these previous works by employing a validated measure of ART exposure not based on self-report, including both ART-naive and ART-exposed periods from people who use illicit drugs recruited from community settings and followed for more than 4000 person-years, and considering all major forms of substance use through discrete time-varying measures.

Like the earlier works by Baum *et al.*[16] and Carrico *et al.*[17], we observed a positive effect of crack cocaine use on HIV viral load independent of exposure to ART. However, given the observational nature of our study design and the possibility of error in our variables and unmeasured confounding, we cannot conclude there is a direct biological relationship between exposure to crack cocaine and swifter HIV disease progression. For example, future research should test the possibility that incomplete ART adherence resulting from crack cocaine use produces resistant viral forms leading to virologic failure and uncontrolled viremia. Beyond that indirect pathway, our findings are consistent with some existing

preclinical evidence and the hypothesis that there may be biological effects of crack cocaine on HIV viral load that function independently of ART exposure [26–28]. For example, a 2014 study by Pandhare *et al.*[27] demonstrated that acute cocaine exposure enhanced HIV-1 mediated $CD4^+$ T-cell apoptosis in ex-vivo assays, with an increased generation of reactive oxygen species (ROS being proposed as the underlying pathological mechanism.) However, this study was limited by the fact that only powder cocaine was studied, the authors included levels of cocaine and virus (>100 000 copies/ml) beyond typical physiological values in an experimental setting and only acute exposure was assessed. Other studies on synergistic neurotoxicity of cocaine and HIV-1 membrane proteins support a possible mechanism of crack cocaine mediated HIV disease progression with increased ROS and dysregulation of other cellular signalling pathways [26,28].

Interestingly, our analyses produced divergent findings on the effects of crack cocaine vs. powder cocaine on HIV viral load. Although both any and daily use of crack cocaine was linked with higher HIV viral load in both crude and adjusted models, only daily powder cocaine use was significantly linked to HIV viral load in the bivariate analysis (but not in the multivariable model.) Our study is the first, to our knowledge, to longitudinally investigate the separate effects of the two major forms of cocaine (in addition to other psychoactive substances) on HIV disease progression. Our divergent results might, in part, be a product of lower rates of powder cocaine use in this group, although at least some use was reported in more than 1000 study interviews (12% of all interviews.) Although both forms have similar pharmacokinetics [13,29], important differences between powder cocaine and crack cocaine – in terms of primary route of administration [29], rate of onset [30], dependence liability [31], neuropsychological impact [32] and the social/structural correlates of users [33] – have been identified. Future work could investigate the contribution of these factors to HIV disease progression.

In the multivariable models, we included nonsubstance use covariates (i.e. sex, age, homelessness, IDU, $CD4^+$ cell count and ART exposure) to adjust the estimates of noninjection substance use on HIV viral load. Although their effect measures cannot assumed to be unbiased estimates of their relationship to HIV viral load, some tentative comments are possible. First, homelessness was significantly associated with greater HIV viral load in both crude analyses and multivariable models also adjusted for ART exposure. Although homelessness has long been identified as an important barrier to optimal ART adherence [34], there are few longitudinal analyses of homelessness and HIV viral load that incorporate ART-exposed and ART-naive periods. As our findings are consistent with an effect on HIV independent of exposure to ART, future research could investigate host-related factors associated with homelessness for links to elevated HIV viral load. One possible area of inquiry could be food security, as hunger and lower BMI are prevalent among people experiencing homelessness and have been linked to poorer virologic response independent of ART adherence [35–37], including in a cross-sectional study of 104 homeless and marginally housed people receiving ART in the United States [37].

In contrast to a wealth of evidence detailing the deleterious impact of alcohol on the health of people living with HIV [38–41], we did not observe significant relationships between either measure of alcohol use and HIV viral load in either crude or adjusted analyses. Although the

evidence base for the impact of alcohol use among HIV-positive people who use illicit drugs is scant, alcohol use (and alcohol dependence) has been linked to deleterious HIV disease progression. For example, a systematic review of 53 clinical studies concluded the majority (77%) found a negative association between alcohol and engagement in the HIV cascade of care [41]. Beyond the relationships between alcohol exposure (both acute and chronic) and HIV progression-related risk factors (e.g. impaired decision making, depression and nonadherence to ART), some studies have also described deleterious biological impacts of frequent alcohol consumption among people living with HIV, including higher rates of viral replication [11], damage to relevant immune processes [40] and impaired ART metabolism [42].

The current study builds on previous work by identifying a positive longitudinal effect of crack cocaine use in a dose-dependent fashion on HIV viral load independent of exposure to ART and other relevant confounders, including other substance use. Although strengths of the study include its prospective design involving more than 800 individuals with prevalent polysubstance use and linked dispensation data on ART exposure, caution should be taken in interpreting the results. First, substance use patterns relied on self-report, as we lacked objective measures of exposure to substances (e.g. urine drug screens) over the entire study period. However, self-reported data among PWUD generally provide reliable and valid measures of drug use behaviours [43]. Second, our measure of ART exposure was derived from ART dispensation records from the local HIV treatment registry. Although this measure of ART dispensation has been shown to predict HIV viral load suppression and survival [44,45], ingestion was not directly observed and we cannot exclude the possibility of error in this measure. Future research could better investigate the relationships between substance use, HIV disease progression and ART exposure by employing biological measures, such as the plasma concentrations of antiretroviral agents. As this is an observational design, there is a potential that residual confounding may have influenced the results. Also, ACCESS is not a random sample and the findings may not be generalizable to PWUD in other settings. Finally, although several substance were used in approximately half of all study interviews [e.g. crack cocaine (5226 interviews, 60%), alcohol (3953, 45%), cannabis (4227, 49%)], our analyses may have been underpowered to detect small effects associated with other substance types [e.g. opioids (983, 11%), powder cocaine (1017, 12%) and methamphetamine (1035, 12%)].

In conclusion, although poor ART adherence has been identified as a primary driver of HIV disease progression in PWUD, our study and others indicate that crack cocaine use may be an important determinant of HIV viral load response, independent of ART exposure. This suggests that there may be a biological impact of crack-cocaine on HIV disease progression. The specific mechanism underlying this association warrants future investigation in HIV-positive PWUD to reduce the morbidity and mortality associated with HIV disease progression in an already marginalized population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics of 843 HIV-positive illicit drugs users stratified by patterns of noninjection substance use in the last 6 months.

Characteristics		All 843 (100%)	Crack cocaine use 659 (78%)	Opioid use 157 (19%)	Cocaine use 141 (17%)	Methamphetamine use 138 (16%)	Alcohol use 446 (53%)	Cannabis use 481 (57%)
Sex (*n*, %)	Male	566 (67%)	433 (66%)	102 (65%)	102 (72%)	104 (75%)	300 (67%)	353 (73%)
Age	Median (IQR)	43 (37–48)	43 (37–48)	43 (36–48)	41 (36–47)	41 (34–48)	44 (37–49)	43 (36–48)
IDU (*n*, %)	Yes	664 (79%)	523 (79%)	137 (87%)	113 (80%)	104 (75%)	330 (74%)	376 (78%)
Substances used	Median (IQR)	2 (2–3)	3 (2–3)	4 (3–4)	4 (3–4)	3 (3–4)	3 (2–4)	3 (2–4)
Homelessness (*n*, %)	Yes	259 (31%)	210 (32%)	52 (33%)	55 (39%)	51 (37%)	128 (29%)	154 (32%)
HIV RNA VL (log_{10}(copies/ml))	Median (IQR)	3.1 (1.7–4.5)	3.3 (1.77–4.5)	2.7 (1.7–4.2)	3.5 (1.7–4.4)	2.3 (1.5–4.1)	2.5 (1.6–4.4)	2.7 (1.7–4.4)
$CD4^+$ cell count (cells/(μl)	Median (IQR)	340 (210–500)	335 (206–480)	330 (208–510)	352 (206–473)	430 (266–620)	345 (210–492)	362 (223–520)
ART exposure (days)	Median (IQR)	180 (117–180)	180 (111–180)	180 (109–180)	180 (105–180)	180 (101–180)	180 (118–180)	180 (118–180)

ART, antiretroviral therapy.

Table 2.

Characteristics of 843 HIV-positive illicit drug users during 8698 study interviews stratified by noninjection substance use in the last 6 months.

Characteristics		All 8698 (100%)	Crack cocaine use 5226 (60%)	Opioid use 983 (11%)	Cocaine use 1017 (12%)	Methamphetamine use 1035 (12%)	Alcohol use 3953 (45%)	Cannabis use 4227 (49%)
Sex (*n*, %)	Male	5785 (67%)	3367 (64%)	658 (67%)	686 (67%)	758 (73%)	2721 (69%)	3140 (74%)
Age (years)	Median (IQR)	47 (41–53)	47 (41–53)	47 (40–52)	46 (40–52)	46 (40–51)	47 (42–53)	47 (41–52)
IDU (*n*, %)	Yes	5090 (59%)	3360 (64%)	734 (75%)	839 (82%)	716 (69%)	2388 (60%)	2624 (62%)
Substances used	Median (IQR)	2 (1–3)	2 (2–3)	3 (3–4)	3 (2–4)	3 (2–4)	3 (2–3)	3 (2–3)
Homelessness (*n*, %)	Yes	1193 (14%)	845 (16%)	199 (20%)	198 (19%)	181 (17%)	568 (14%)	633 (15%)
HIV RNA VL (log_{10}(copies/ml))	Median (IQR)	1.6 (1.5–3.3)	1.7 (1.5–3.6)	1.7 (1.5–3.7)	1.7 (1.5–3.7)	1.5 (1.5–2.9)	1.6 (1.5–3.2)	1.6 (1.5–3.3)
$CD4^+$ cell count (cells/μl)	Median (IQR)	375 (240–547)	360 (229–523)	380 (241–566)	352 (227–500)	445 (283–623)	377 (240–548)	375 (240–550)
ART exposure (days)	Median (IQR)	180 (143–180)	180 (140–180)	180 (133–180)	180 (135–180)	180 (138–180)	180 (138–180)	180 (140–180)

ART, antiretroviral therapy.

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Table 3.

Generalized linear mixed-effects estimates of substance use and other factors associated with HIV-1 RNA viral load (log10copies/ml plasma).

Covariate		Univariate β (95% confidence interval)	Multivariable model: Crack cocaine use β (95% confidence interval)	Multivariable model: Opioid use β (95% confidence interval)	Multivariable model: Cocaine use β (95% confidence interval)	Multivariable model: Methamphetamine use β (95% confidence interval)	Multivariable model: Cannabis use β (95% confidence interval)	Multivariable model: Alcohol use β (95% confidence interval)
Crack cocaine[a]	Any	0.312 (0.255–0.369)	0.068 (0.022–0.113)	0.065 (0.019–0.11)	0.067 (0.021–0.112)	0.072 (0.027–0.117)	0.075 (0.029–0.121)	0.070 (0.025–0.116)
	≥ Daily	0.681 (0.608–0.753)	0.163 (0.104–0.221)	0.158 (0.099–0.217)	0.163 (0.104–0.222)	0.170(0.112–0.229)	0.174 (0.115–0.233)	0.163 (0.104–0.222)
Opioids[a]	Any	0.143 (0.066–0.220)		0.028 (−0.033 to 0.089)	0.024 (−0.036 to 0.085)			
	≥ Daily	0.045 (−0.146 to 0.235)		0.018 (−0.13 to 0.165)	0.008 (−0.139 to 0.155)			
Cocaine[a]	Any	0.065 (−0.035 to 0.165)			0.003 (−0.075 to 0.081)			
	≥ Daily	0.165 (0.063–0.267)			−0.020 (−0.099 to 0.06)			
Methamphetamine use[a]	Any	−0.071 (−0.156 to 0.014)		−0.028 (−0.094 to 0.038)		−0.024 (−0.09 to 0.041)	−0.019 (−0.085 to 0.048)	−0.021 (−0.087 to 0.045)
	≥ Daily	−0.281 (−0.457 to −0.105)		−0.121 (−0.257 to 0.015)		−0.123 (−0.259 to 0.012)	−0.111 (−0.247 to 0.026)	−0.117 (−0.252 to 0.019)
Cannabis[a]	Any	0.067 (0.004–0.131)		−0.003 (−0.053 to 0.046)	−0.006 (−0.055 to 0.043)		0.004 (−0.047 to 0.054)	
	≥ Daily	−0.025 (−0.104 to 0.054)		−0.063 (−0.122 to −0.003)	−0.067 (−0.127 to −0.007)		−0.059 (−0.119 to 0.002)	
Alcohol[a]	Any	0.002 (−0.053 to 0.057)					−0.037 (−0.081 to 0.006)	−0.042 (−0.085 to 0.001)
	≥ Daily	−0.021 (−0.135 to 0.093)					−0.039 (−0.128 to 0.050)	−0.049 (−0.137 to 0.038)
Sex	Male	−0.205 (−0.336 to −0.074)					0.050 (−0.039 to 0.139)	
Age	Per year	−0.082 (−0.088 to −0.076)	−0.023 (−0.027, −0.019)	−0.023 (−0.027 to −0.019)	−0.023 (−0.027 to −0.019)	−0.025 (−0.029 to −0.021)	−0.025 (−0.029 to −0.021)	−0.023 (−0.027 to −0.019)
Homelessness[a]	Yes	0.626 (0.558–0.694)	0.189 (0.135–0.243)	0.188 (0.134–0.243)	0.188 (0.134–0.243)			0.189 (0.135–0.244)
IDU[a]	Yes	0.327 (0.269–0.386)	0.119 (0.074–0.165)	0.120 (0.074–0.166)	0.120 (0.074–0.166)	0.128 (0.082–0.173)	0.127 (0.081–0.173)	0.124 (0.079–0.170)

Covariate		Univariate β (95% confidence interval)	Multivariable model: Crack cocaine use β (95% confidence interval)	Multivariable model: Opioid use β (95% confidence interval)	Multivariable model: Cocaine use β (95% confidence interval)	Multivariable model: Methamphetamine use β (95% confidence interval)	Multivariable model: Cannabis use β (95% confidence interval)	Multivariable model: Alcohol use β (95% confidence interval)
$CD4^+$ cell count[b]	Per 100 cells/μl	−0.072 (−0.098 to −0.045)	0.086 (−0.104 to −0.068)	−0.084 (−0.102 to −0.066)	−0.085 (−0.103 to −0.067)	−0.085 (−0.104 to −0.067)	−0.084 (−0.102, −0.066)	−0.085 (−0.102 to −0.067)
ART exposure[a]	Per 100 days	−1.199 (−1.231 to −1.168)	−1.102 (−1.135 to −1.069)	−1.101 (−1.135 to −1.068)	−1.102 (−1.135 to −1.069)	−1.118 (−1.15 to −1.085)	−1.119 (−1.152 to −1.087)	−1.102 (−1.135 to −1.069)

ART, antiretroviral therapy.

[a]Last six months.

[b]Current status.

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