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Methadone maintenance therapy and viral suppression among HIV-infected opioid users: the impacts of crack and injection cocaine use

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Abstract

Background—Methadone maintenance therapy (MMT) is associated with improved HIV treatment outcomes among people who use drugs (PWUD). The extent to which these benefits are sustained in the context of ongoing cocaine use is unclear. We assessed differential impacts of MMT on HIV viral load (VL) suppression in relation to discrete patterns of cocaine use.

Methods—Data was drawn from ACCESS, a prospective cohort of HIV-positive PWUD in Vancouver, Canada. Generalized linear mixed-effects were used to model the independent effect of MMT on VL suppression across strata of frequency of cocaine injection and crack smoking (daily versus <daily), after adjustment for confounders.

Results—The analysis included 397 HIV-positive opioid users who completed 1 study interview between 2005 and 2014. At baseline, 304 (77%) reported participation in MMT, 37 (9%) daily cocaine injection, and 158 (40%) daily crack smoking. In adjusted analyses, MMT remained independently associated with increased odds of VL suppression in both strata of crack smokers (AOR=3.11, 95% CI: 1.86–5.21 and AOR=1.48, 95%CI: 1.04–2.09, for daily and <daily smokers, respectively), and among <daily cocaine injectors (AOR=1.88, 95%CI 1.38–2.56), but not among daily cocaine injectors (AOR=1.37, 95%CI 0.53–3.49). Longer retention on MMT was positively associated with VL suppression in all strata of cocaine injection and crack smoke.

Conclusions—Exposure to MMT was associated with increased odds of VL suppression among HIV- positive opioid users regardless of crack use. However, this beneficial effect of MMT was lost among frequent cocaine injectors with shorter retention on MMT.

Keywords

opioid substitution treatment; methadone maintenance therapy; antiretroviral therapy; cocaine; viral suppression; opioid use disorder

1. Introduction

The use of antiretroviral therapy (ART) in the control of the HIV pandemic is now firmly established (Joint United Nations Programme on HIV/AIDS, 2014). High quality evidence indicates that prompt initiation of ART is associated with reduced mortality and morbidity, and secondarily with reduced HIV transmission (Cohen et al., 2011; Grinsztejn et al., 2014; Insight Start Study Group et al., 2015; Rodger et al., 2014; Temprano Anrs Study Group et al., 2015). As such, guidelines for both high-income and resource-limited settings now recommend initiating ART immediately following diagnosis of HIV infection regardless of CD4 cell count (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015; World Health Organization, 2016).

Unfortunately, not all people living with HIV/AIDS PLWH have benefited equally from advancements in HIV/AIDS treatment. In particular, research shows that people who use drugs (PWUD) experience lower rates of access to ART, with consequent sub-optimal virological, clinical and transmission outcomes (Kamarulzaman and Altice, 2015; Milloy et al., 2012). Co-morbid mental illnesses, ongoing substance use, as well as social-structural factors, such as stigma, unstable housing, and criminalization, have been identified as factors compromising PWUD's engagement in HIV care (Kamarulzaman and Altice, 2015; Milloy et al., 2012).

Despite these challenges, recent studies have documented improved HIV-related outcomes among opioid-dependent individuals enrolled in opioid substitution treatment (OST) programs, including increased access to and adherence to ART, and decreased HIV incidence (Ahamad et al., 2015; Altice et al., 2011; Lappalainen et al., 2015; Nosyk et al., 2015a; Palepu et al., 2006; Wood et al., 2005). While the potential of OST as a platform to facilitate engagement of PWUD in HIV care is encouraging, the extent to which these benefits are sustained in the context of ongoing cocaine use is unclear. This is particularly relevant for a number of reasons. First, there is substantial evidence of the deleterious impact of cocaine use on adherence to ART and some data describing hastened HIV disease progression among active cocaine users (Carrico, 2011). Second, cocaine use is highly prevalent among opioid-dependent individuals entering OST (Gonzalez et al., 2013; Sullivan et al., 2011). And third, there are no effective pharmacotherapies for the treatment of cocaine use disorders (Shorter et al., 2015)

Thus, given the critical role of sustained viral suppression in maximizing the individual- and population-level benefits of ART, the aim of this study was to evaluate whether the effect of methadone maintenance treatment (MMT) on viral suppression differs among opioid users

with distinct patterns of cocaine use. We were interested in investigating not only the impacts of high intensity cocaine use (i.e., daily use), but also on potential differences between routes of administration (i.e., crack smoking and cocaine injection).

2. Materials and methods

2.1. Study design and population

Data for this study were drawn from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing prospective cohort of HIV-positive adults who use illicit drugs in Vancouver, Canada that began recruitment in 2005. Eligibility criteria include HIV-seropositivity, age ≥ 18 years, residency within greater Vancouver, and having used illicit drugs other than cannabis in the previous month. Participants are recruited through snowball sampling and extensive street outreach with a focus in the Downtown Eastside neighborhood, an area with an open drug market and high levels of illicit drug use, poverty and HIV infection. Sampling and recruitment procedures have been described in detail previously (Strathdee et al., 1998; Wood et al., 2008).

After providing written informed consent, at baseline and on a semi-annual basis thereafter participants complete an interviewer-administered questionnaire that collects socio-demographic information, drug use patterns, health care access and utilization, including HIV and addiction care, as well as other relevant exposures. At each of these visits, participants provide blood samples for serological testing (e.g., HCV antibodies) and are examined by a study nurse, who can provide referrals to additional health services when needed. In addition, as has been described elsewhere (Wood et al., 2008), information gathered at each semi-annual visit is augmented by confidential data linkages with the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) Drug Treatment Program, which provides HIV care, including free ART to all PLWH in the province of British Columbia. These linkages allow for a complete longitudinal clinical and laboratory profile for each participant, including CD4 counts, plasma viral load, and ART dispensation. Participants receive CAD\$ 30 stipend at each study visit. The ACCESS study has received ethical approval by the University of British Columbia/Providence Health Care Research Ethics Board.

For this analysis, we included participants who reported any history of opioid use, and who were ART exposed at enrollment. ART-naïve participants who subsequently initiated ART were included from the next follow-up interview forward. We further restricted our analytical sample to participants who had at least one VL measure and one CD4 measure within ± 180 days of the earliest interview.

2.2. Measures

The primary outcome of interest for these analyses was a time-updated measure of VL. Viral suppression was defined as having a HIV plasma viral load < 50 copies/mL (yes versus no) in the previous six months. In the case of multiple VL measurements within a six-month follow-up period, the median of all the observations was utilized. This number was then

used to dichotomize participants at $\leq$ or $>$ 50 c/mL as virally suppressed or not for that period.

The primary explanatory variable was a time-varying measure of enrollment in a methadone maintenance program (MMT) for the treatment of opioid use disorders in the six-month period preceding the study interview (yes vs. no). Given that the main objective of this study was to explore whether ongoing cocaine use modified the effect of MMT on viral suppression among HIV-positive opioid users, we ran two separate analyses, considering the two common patterns of cocaine use among our study population: (a) cocaine injection (daily versus $<$ daily) and (b) crack-cocaine smoking (daily versus $<$ daily).

We also considered several secondary covariates that in previous analyses have been shown to affect the relationship between engagement in MMT and viral suppression (Kerr et al., 2012; Lappalainen et al., 2015; Richardson et al., 2015). Time-fixed variables of interest at baseline included: age (per 10 years older); gender (male versus female); ethnicity (Caucasian versus non-Caucasian); highest educational attainment (high school or postsecondary education vs. less than high school completion); and depressive symptomatology (defined as a Center for Epidemiologic Studies Depression Scale [CES-D] score $\geq$ 16, yes versus no) (Radloff, 1977). Time-varying variables included frequent heroin injection (daily versus $<$ daily); heavy alcohol use ($\geq$ 4 drinks/day versus $<$ 4 drinks/day); unstable housing (yes versus no); incarceration (yes versus no); involvement in sex work (yes versus no); and employment (yes versus no). Unstable housing was defined as 1 night in a single room occupancy hotel, shelter, or hostel, living on the street or having no fixed address. Employment was defined as income generation from regular job, temporary job, or self-employed. All time-varying variables were time-updated at each semi-annual follow-up visit and refer to the six-month period prior to the interview, with the exception of the assessment of depressive symptoms, which refers to the week prior to the interview. Clinical covariates included year of ART initiation (per year increase) and VL at ART initiation (per log₁₀ c/mL increase). Cocaine injection and crack-cocaine use were also considered as potential confounders in the evaluation of the other pattern of cocaine use.

2.3. Statistical analyses

As a preliminary analysis, we examined the baseline characteristics of study participants stratified by enrolment in a MMT program within the six months prior to enrolment. Categorical variables were analyzed using the Pearson's chi-squared test (or Fisher's exact test in the presence of small cell counts) and continuous variables were analyzed using the Wilcoxon rank sum test. Next, we estimated the bivariable relationship between the primary explanatory variable (i.e., enrollment in a MMT program) and each secondary covariate on achievement of VL suppression. We used generalized linear mixed-effects models (GLMM) with a logit-link function to account for repeated measurements from the same participants over time.

To assess the independent effect of MMT on VL suppression, and to investigate whether different patterns of cocaine use modified this relationship, we followed a procedure recommended by Knol and VanderWeele (Knol and VanderWeele, 2012; Knol et al., 2011). First, we constructed multivariable models and calculated odds ratios (OR) for each stratum

of MMT and cocaine use (separately for cocaine injection and crack-cocaine use) with a single reference category. We chose the group of participants who did not report being on MMT but using cocaine as the reference stratum because we hypothesized *a priori* it was associated with the lowest probability of VL suppression. We then estimated the effects of MMT across strata of cocaine injection and crack-cocaine use. To build the multivariable models, all the secondary covariates that were associated with VL suppression in bivariable analyses at a p-value <0.10 were considered as potential confounders and included in the final model.

We conducted tests for modification of the effect of MMT on VL suppression by different patterns of cocaine use on both the additive and multiplicative scale. For testing on the additive scale, we calculated the relative excess risk due to interaction (RERI) and 95% confidence interval (CI), using the delta method described by Hosmer and Lemeshow (Hosmer and Lemeshow, 1992). For testing on the multiplicative scale, we calculated the ratio of OR in the strata of either cocaine injection or crack-cocaine use (RERI = 0 means no interaction, while RERI > or < 0 means positive or negative interaction in the additive scale, respectively. Similarly, a ratio of OR = 1 means no interaction, while > 1 or < 1 means positive or negative interaction in the multiplicative scale, respectively.) From a public health perspective, the additive scale is more relevant as it provides indication of whether the effect of MMT on viral suppression differs for individuals with different patterns of cocaine use.

To assess the robustness of our models, we conducted a series of sensitivity analyses. First, to further examine the impact of poly-drug use, we included additional variables referring to at least daily use (i.e., frequent use) of the following drugs and modes of administration: non-injection heroin, prescription opioids injection, non-injection prescription opioids, methamphetamine injection, and cannabis use. Second, to further investigate the impacts of patterns of MMT, we constructed two models using as primary explanatory variables high doses of MMT (i.e., 100mg/day) and maximum consecutive length on MMT, respectively (Lappalainen et al., 2015; Roux et al., 2009). We chose to dichotomize MMT doses at 100mg/day as doses above this threshold have been associated with improved HIV and drug treatment outcomes (Lappalainen et al., 2015). For the analysis of retention on MMT, we dichotomize the maximum consecutive length at the sample median value. Our fourth and last sensitivity analysis evaluated a higher cut-off of viral suppression (i.e., <200 copies/mL) as primary outcome. All statistical analyses were performed using the SAS software version 9.4 (SAS, Cary, NC), and all p-values are two-sided.

3. Results

Between December 2005 and May 2014, 847 individuals were enrolled in the ACCESS cohort. Among the 434 self-reported opioid users recruited, 397 met the eligibility criteria, and were thus included in the present analysis. Baseline characteristics of study participants stratified by enrollment in a MMT program at baseline are presented in Table 1. The median age of the study sample was 41 (Interquartile range [IQR] 36–47), and 234 (59%) were male. At baseline, 304 (77%) reported being enrolled in a MMT program, of whom approximately half (n=147) were receiving MMT doses 100mg/day. In addition, 37 (9%) participants reported injecting cocaine and 158 (40%) smoking crack-cocaine at least daily

in the previous six months. Median consecutive length on MMT was 17.9 months (IQR 7.6–33.6), with no significant differences among strata of cocaine injection and crack use. Overall, 106 participants (27%) reported no use of opioids in the last six months. Less than daily crack users were more likely to be abstinent from opioids (compared to more frequent users, 35% vs. 15%, $P<0.001$), but no statistically significant differences were observed between the 2 categories of cocaine injection (27% vs. 16%, $P=0.130$).

The median duration of follow-up per participant was 50.3 (IQR 24.3–80.0) months, resulting in a total of 1679.1 person-years of follow up. Over the study period, of a total of 3176 observations, 2015 (63%) were characterized by viral suppression, with 346 (87%) participants achieving at least one episode of viral suppression. As shown in Table 2, in unadjusted analyses, participants enrolled in a MMT program had increased odds of achieving viral suppression (Odds Ratio [OR] = 1.99, 95% Confidence interval [CI] 1.49–2.66), while frequent crack-cocaine smokers had decreased odds (OR = 0.37, 95% CI: 0.29–0.48).

In multivariable GLMM, MMT remained independently and positively associated with viral suppression among less than daily cocaine injectors (Adjusted Odds Ratio [AOR] = 1.88, 95%CI: 1.38–2.56), but not among individuals injecting cocaine more frequently (AOR = 1.37, 95%CI: 0.53–3.49) (Table 3). Tests for effect modification in both the additive and multiplicative scale confirmed this tendency towards a decreased effect of MMT on daily cocaine injectors, although this was not statistically significant (p -value > 0.05).

With regard to crack cocaine use, although there was a significant positive association between MMT enrolment and viral suppression within both strata of crack-cocaine use, this effect was larger among participants who smoked crack at least daily than among those who did not (AOR = 3.11, 95% CI 1.86–5.21 vs. AOR = 1.48, 95%CI 1.04–2.09) (Table 4). Tests for effect modification showed a significant interaction term in the multiplicative scale (p -value = 0.013)

Sensitivity analyses yielded similar results to the main analysis. MMT was associated with increased odds of viral suppression among less frequent cocaine injectors (but not among daily cocaine injectors) and both categories of crack users when additional drug use variables were included in the model (sensitivity analysis 1) or when evaluating a higher cut-off of viral suppression as primary outcome (sensitivity analysis 4). Similar results were observed when investigating the impacts of high doses of MMT (sensitivity analysis 2). Interestingly, the model examining retention on MMT (sensitivity analysis 3) showed that longer consecutive time on MMT was associated with increased odd of viral suppression in all strata of cocaine use, including frequent cocaine injectors (AOR = 4.20, 95%CI 1.66–10.60). Multivariable models for each of the four sensitivity analyses for both cocaine injection and crack smoke are presented in the supplementary appendix (Tables S1–S8).

4. Discussion

In this longitudinal study of HIV-positive opioid users, we found that the effect of MMT on VL suppression differed in relation to distinct patterns of cocaine use. Specifically, while

enrollment in a MMT program was associated with increased odds of VL suppression among less than daily cocaine injectors, this beneficial effect of MMT was lost among more frequent cocaine injectors. However, for frequent cocaine injectors who were retained on MMT for longer consecutive periods a positive impact of MMT on viral suppression was also observed. In addition, crack cocaine use did not undermine the positive impact of MMT on viral suppression, and unexpectedly, we observed a greater positive effect of MMT on viral suppression among daily crack cocaine smokers when compared to less frequent crack cocaine smokers.

There is growing evidence indicating that HIV-positive opioid dependent individuals enrolled in OST have superior HIV/AIDS treatment outcomes, including improved rates of VL suppression (Altice et al., 2011; Lappalainen et al., 2015; Nosyk et al., 2015a; Nosyk et al., 2015b; Wood et al., 2005). It has been hypothesized that this may be due to the stabilization afforded by reduced opioid use and dependence symptoms (e.g., drug withdrawal and craving) and reduced time and effort in procuring opioids (e.g., through involvement in drug scenes and illegal income generation activities), as well as increased contact with healthcare systems (Nosyk et al., 2015a; Palepu et al., 2006). Yet there is limited and conflicting evidence regarding whether the positive impact of OST on HIV-treatment outcomes are similarly observed among dual opioid/cocaine-dependent individuals.

Previous studies have suggested that cocaine use is associated with suboptimal outcomes from treatment for opioid addiction and HIV/AIDS (Azar et al., 2015; Lucas, 2011; Sullivan et al., 2011; Williamson et al., 2006). However, to our knowledge, only two studies have previously investigated the impact of ongoing cocaine use on HIV treatment outcomes among HIV-infected opioid dependent individuals enrolled in OST programs, and these showed conflicting results (Gonzalez et al., 2013; Sullivan et al., 2011). In the North American multisite BHIVES collaboration, ongoing cocaine use did not impact ART adherence of patients receiving buprenorphine/naloxone for their opioid addiction (Sullivan et al., 2011). Conversely, Gonzalez *et al.* found that current cocaine use was significantly associated with decreased ART adherence among HIV-infected individuals enrolled in opioid treatment in Boston, MA (Gonzalez et al., 2013). Of note, neither of these studies assessed differential impacts of distinct patterns of cocaine use, including mode (injected versus smoked or snorted) and frequency (< daily versus daily) of administration.

Our finding that daily cocaine injectors did not have equally improved VL outcomes from MMT is expected and of concern. The need for frequent injections – due to the short half-life of cocaine – may contribute to an unstable lifestyle, where the acquisition and use of cocaine may be prioritized over any other needs, including adherence to ART (Kerr et al., 2012). Importantly, among daily cocaine injectors, longer retention in MMT was associated with increased odds of viral suppression. This finding suggests that frequent cocaine injectors who are able to be retained in MMT for longer periods of time may have distinct resilience profiles than those who are not, that may also facilitate adherence to ART. Future research is needed to better understand what enables some cocaine users to be retained in MMT. In addition to behavioural and psychological factors that may explain reduced ART adherence and consequent higher levels of detectable VL among active cocaine injectors,

emerging preclinical and clinical data reveal that frequent stimulant use may enhance HIV replication and immune activation independent of ART non-adherence, suggesting a potential direct role of cocaine on HIV disease progression (Baum et al., 2009; Carrico, 2011; Cook, 2011; Kapadia et al., 2005). Cocaine use has also been associated with increased HIV risk behavior, including syringe sharing and unprotected sex (Hudgins et al., 1995; Lloyd-Smith et al., 2009; Morin et al., 2007; Tyndall et al., 2003). Thus, these suboptimal virological outcomes in the context of the need of frequent injections and elevated HIV risk behavior may amplify the risk of HIV transmission to injection- and sexual-partners of people who inject cocaine. Collectively, these findings highlight the need for research that identifies effective pharmacotherapies to treat cocaine use disorders, as well as individual and structural interventions that promote ART adherence and the reduction of drug-related harm. In this context, given its promising results in clinical trials, contingency management based interventions may play a role. However, contingency management associated costs and other feasibility barriers (e.g., need for frequent urine drug screens) make their implementation in clinical settings challenging (Farronato et al., 2013).

Interestingly, we found a trend towards a larger effect of MMT on viral suppression among daily crack-cocaine smokers when compared with less frequent smokers or non-smokers. This is somewhat unexpected given numerous previous studies showing lower ART adherence among crack-cocaine users (Baum et al., 2009; Sharpe et al., 2004), and these findings might suggest that crack using individuals enrolled in addiction treatment (i.e., OST) may constitute a unique sub-group. It may be the case that among opioid users engaged in MMT, crack-cocaine is being used as a strategy to reduce the use of other harmful substances that have also been associated with poorer virological outcomes, such as heroin, cocaine injecting and alcohol abuse. Additional research is needed to better understand these results and the combination of interventions that are best suited to address the well-documented health and social harms associated with crack-cocaine use disorders (DeBeck et al., 2011; DeBeck et al., 2009; Fischer et al., 2008; Fischer et al., 2006; McNeil et al., 2015). This again underscores the need for multi-level approaches, including research for effective pharmacotherapies to treat this form of addiction, as well as harm reduction opportunities (e.g., safe smoking facilities and distribution of safer smoking kits), and other social support interventions in order to improve the health and wellbeing of people who smoke crack-cocaine (Fischer et al., 2006; McNeil et al., 2015).

Several limitations of this study should be noted. First, our study sample was not randomly selected, and thus might not be representative of the larger population of HIV-positive opioid dependent individuals in Vancouver or other settings. Second, many measures, including our primary explanatory variable (i.e., enrollment in MMT) and cocaine use, relied on self-reported data, which might be subject to social-desirability bias and underreporting. However, previous research has shown PWUD's reports of drug use and addiction treatment to be reliable (De Irala et al., 1996; Langendam et al., 1999). In addition, our primary outcome of interest, VL suppression, is based on objective laboratory data, and there is no reason to believe that there was differential reporting of participation in MMT or cocaine use based on participant's VL status. Third, given the observational nature of this study, and despite the utilization of multivariable statistical approaches, we cannot exclude the possibility of residual unmeasured confounding. Fourth, the current analytic approach does

not allow us to tease out relative contributions of behavioral and biological pathways and lower rates of viral suppression among frequent cocaine injectors. Fifth, the absence of a positive association between MMT and VL suppression during periods of at least daily cocaine injection may have been the result of low statistical power. That said, while there were only relatively few frequent cocaine injectors at baseline, the use of all the available longitudinal data might have resulted in increased power. Of note, the bivariable GLMM result was not significant either, and neither this confidence interval nor the one for the adjusted analysis were particularly large. Finally, the study design does not allow us to determine the exact temporal relationship between enrollment in MMT and VL suppression within any six-month period.

In summary, in this long-running prospective cohort of HIV-infected PWUD recruited from community settings, we found that participation in MMT was associated with increased odds of viral suppression among opioid users regardless of crack-cocaine use. However, our results also showed that daily cocaine injectors did not experience the beneficial impact of MMT on viral suppression. Importantly, frequent cocaine injectors who were retained on MMT for longer periods of time also enjoyed the positive impact of MMT on viral suppression. This is relevant to public health, as sustained VL suppression is critical not only to improve the health and well-being of PLWH, but also to reducing the risk of HIV transmission. Collectively, results from this study further support calls from the World Health Organization (World Health Organization, 2014) and others to expand access to low-threshold OST as a way to facilitate engagement in HIV care and improve addiction and HIV outcomes among HIV-infected opioid users. In addition, our findings underscore the urgent need to identify novel and effective pharmacotherapies for the treatment of cocaine use disorders, as well as social-structural interventions to support engagement in addiction and HIV care for this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of 397 HIV-positive opioid users stratified by enrolment in MMT at baseline, Vancouver, Canada (2005–2014)

Characteristic	Total, n (%) <i>(N = 397)</i>	Enrolment in MMT, n (%)		<i>p</i> - value
		Yes (<i>n</i> = 304)	No (<i>n</i> = 93)	
Individual-level factors				
Age (median, IQR)	41 (36–47)	42 (36–47)	40 (35–47)	0.400
Male gender	234 (58.9)	174 (57.2)	60 (64.5)	0.212
Caucasian ethnicity	226 (56.9)	182 (59.9)	44 (47.3)	0.032
High school education or higher	178 (44.8)	138 (45.4)	40 (43.0)	0.525
Daily cocaine injection [*]	37 (9.3)	29 (9.5)	8 (8.6)	0.786
Daily crack smoking [*]	158 (39.8)	120 (39.5)	38 (40.9)	0.811
Daily heroin injection [*]	77 (19.4)	44 (14.5)	33 (35.5)	<0.001
Heavy alcohol drinking [*]	8 (2.0)	6 (2.0)	2 (2.1)	1.000
Depressive symptoms [†]	226 (56.9)	175 (57.6)	51 (54.8)	0.532
Daily non-injection heroin [*]	5 (1.3)	120 (39.5)	38 (40.9)	0.811
Daily PO injection [*]	16 (4.0)	120 (39.5)	38 (40.9)	0.811
Daily non-injection PO [*]	4 (1.0)	120 (39.5)	38 (40.9)	0.811
Daily methamphetamine injection [*]	16 (4.0)	120 (39.5)	38 (40.9)	0.811
Daily cannabis use [*]	82 (20.7)	120 (39.5)	38 (40.9)	0.811
Year of ART initiation (median, IQR)	2004 (1998– 2009)	2004 (1998– 2009)	2005 (1999– 2008)	0.805
VL (log10 c/mL) at ART initiation (median, IQR) [‡]	4.5 (3.4–5.0)	4.6 (3.4–5.0)	4.1 (3.2–4.7)	0.010
Structural-level factors				
Employment [*]	59 (14.9)	45 (14.8)	14 (15.1)	0.952
Sex work [*]	58 (14.6)	47 (15.5)	11 (11.8)	0.393
Unstable housing [*]	270 (68.0)	203 (66.8)	67 (72.0)	0.404
Incarceration [*]	57 (14.4)	44 (14.5)	13 (14.0)	0.905

MMT, methadone maintenance therapy; PO, prescription opioid; ART, antiretroviral therapy; VL, plasma viral load

* Refers to the 6-month period prior to the baseline interview

† Refers to the 1-week period prior to the baseline interview

‡ in copies/mL

Table 2

Bivariate generalized linear mixed-effects analysis of factors associated with viral suppression among 397 HIV-positive opioid users, Vancouver, Canada (2005–2014)

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p - value
Enrolment in MMT *			
(yes vs. no)	1.99	(1.49 – 2.66)	<0.001
Daily cocaine injection *			
(yes vs. no)	0.77	(0.53 – 1.13)	0.185
Daily crack-cocaine smoking *			
(yes vs. no)	0.37	(0.29 – 0.48)	<0.001
Age			
(per additional 10 years)	2.01	(1.53 – 2.64)	<0.001
Male gender			
(yes vs. no)	1.33	(0.87 – 2.06)	0.192
Caucasian ethnicity			
(yes vs. no)	1.59	(1.02 – 2.47)	0.039
High school education or higher			
(yes vs. no)	0.71	(0.46 – 1.10)	0.123
Daily heroin injection *			
(yes vs. no)	0.39	(0.29 – 0.54)	<0.001
Heavy alcohol drinking *			
(yes vs. no)	1.07	(0.48 – 2.35)	0.876
Daily non-injection heroin			
(yes vs. no)	0.52	(0.15 – 1.80)	0.299
Daily PO injection *			
(yes vs. no)	0.61	(0.37 – 1.01)	0.054
Daily non-injection PO *			
(yes vs. no)	3.70	(0.75 – 18.19)	0.107
Daily methamphetamine injection *			
(yes vs. no)	1.12	(0.57 – 2.20)	0.752
Daily cannabis use *			
(yes vs. no)	1.35	(0.98 – 1.86)	0.063
Depressive symptoms †			
(yes vs. no)	0.91	(0.54 – 1.52)	0.713
Year of ART initiation			
(per year increase)	0.96	(0.77 – 1.19)	0.679
VL at ART initiation ‡			
(per log10 increase)	0.88	(0.72– 1.09)	0.243
Employment *			
(yes vs. no)	1.23	(0.92– 1.66)	0.166

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	<i>p</i> - value
Sex work [*]			
(yes vs. no)	0.59	(0.40 – 0.89)	0.011
Unstable housing [*]			
(yes vs. no)	0.63	(0.48 – 0.81)	<0.001
Incarceration [*]			
(yes vs. no)	0.49	(0.34 – 0.71)	<0.001

MMT, methadone maintenance therapy; PO, prescription opioid; ART, antiretroviral therapy; VL, plasma viral load

^{*} Refers to the 6-month period prior to the interview

[†] Refers to the 1-week period prior to the interview

[‡] in copies/mL

Table 3

Multivariable generalized linear mixed-effects analyses for the association between MMT and viral suppression among 397 HIV-positive opioid users, stratified by frequency of cocaine injection, Vancouver, Canada (2005–2014)

	MMT=No		MMT=Yes		AORs (95% CI) for MMT within strata of frequency of cocaine injection
	Observations with/without viral suppression	AOR (95% CI)	Observations with/without viral suppression	AOR (95% CI)	
Daily cocaine injection	19/32	1.0	134/79	1.37 (0.53–3.49); $P = 0.516$	1.37 (0.53–3.49); $P = 0.516$
< Daily cocaine injection	287/250	0.74 (0.31–1.78); $P = 0.499$	1572/794	1.39 (0.58–3.33); $P = 0.463$	1.88 (1.38–2.56); $P < 0.001$

MMT, methadone maintenance therapy; AOR, adjusted odds ratio; CI, confidence interval

ORs are adjusted for age at baseline, ethnicity, unstable housing, incarceration, sex work, daily heroin injection, daily crack smoke.

Measure of effect modification on additive scale: RERI (95% CI) = 0.28 (−0.57 – 1.13); $P = 0.511$.

Measure of effect modification on multiplicative scale: ratio of ORs (95% CI) = 1.37 (0.53 – 3.60); $P = 0.514$.

Table 4

Multivariable generalized linear mixed-effects analyses for the association between MMT and VL suppression among 397 HIV-positive opioid users, stratified by frequency of crack cocaine use, Vancouver, Canada (2005–2014)

	MMT=No		MMT=Yes		AORs (95% CI) for MMT within strata of frequency of crack-cocaine use
	Observations with/without viral suppression	AOR (95% CI)	Observations with/without viral suppression	AOR (95% CI)	
daily crack-cocaine smoke	48/117	1.0	449/331	3.11 (1.86–5.21); $P < 0.001$	3.11 (1.86–5.21); $P < 0.001$
< daily crack-cocaine smoke	257/168	4.17 (2.39–7.27); $P < 0.001$	1258/544	6.15 (3.66–10.34); $P = < 0.001$	1.48 (1.04–2.09); $P = 0.028$

MMT, methadone maintenance therapy; AOR, adjusted odds ratio; CI, confidence interval

ORs are adjusted for age at baseline, ethnicity, unstably housing, incarceration, sex work, daily heroin injection

Measure of effect modification on additive scale: RERI (95% CI) = -0.13 ($-1.89 - 1.63$); $P = 0.886$.

Measure of effect modification on multiplicative scale: ratio of ORs (95% CI) = 0.47 ($0.26 - 0.85$); $P = 0.013$.