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PRESCRIPTION OPIOID INJECTION AMONG HIV-POSITIVE PEOPLE WHO INJECT DRUGS IN A CANADIAN SETTING

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Abstract

Prescription opioids (POs) are commonly prescribed to patients living with HIV/AIDS, while the illicit use of POs remains a major public health concern throughout Canada and the United States. We sought to identify the prevalence and correlates of PO injection among HIV-positive people who inject drugs (PWID) in Vancouver, Canada, where HIV/AIDS treatment and care is offered at no cost. We examined data from 634 individuals from an ongoing prospective cohort of HIV-positive PWID. Between December 2005 and November 2013, the median prevalence of recent PO injection was 24.2 % [interquartile range (IQR): 21.5–25.8 %]. In a multivariable generalized estimating equation model, Caucasian ethnicity, heroin injection, and drug dealing were positively associated with PO injection, while older age and methadone maintenance treatment were negatively associated with PO injection (all $p < 0.05$). Engagement on antiretroviral therapy was inversely associated with PO injection in a bivariable analysis, but did not remain significant after adjusting for heroin injection. These findings describe a particularly vulnerable sub-group of PWID who may benefit from targeted efforts to both minimize drug-related risk behaviors and support HIV/AIDS treatment.

Keywords

Prescription opioids; people who inject drugs; antiretroviral therapy; treatment as prevention

INTRODUCTION

There has been a substantial increase in the use of prescription opioids (POs) for the treatment of non-cancer pain in the United States (US) and Canada over the previous decade

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[1, 2], including among people living with HIV/AIDS [3]. This surge in PO use has coincided with higher levels of PO-related morbidity and mortality, including PO-attributable overdoses, in the general population [4–6]. Meanwhile, among high-intensity substance-using populations, such as people who inject drugs (PWID), PO use has been linked with injection-related infectious disease, including outbreaks of viral hepatitis among young, inexperienced injectors [7, 8], and—most recently—an HIV outbreak in the US state of Indiana [9]. A growing number of studies have revealed that people who inject POs are often more likely than their non-PO-using peers to engage in risky substance use behaviors (e.g., syringe sharing) [10, 11].

People living with HIV/AIDS are prescribed long-term use of opioids at more than twice the rate of HIV-negative people [12]. The injection of POs has become more frequent among PWID [11, 13], who account for nearly 15 % of new HIV infections in Canada [14]. Despite both the high prevalence of PO use among people living with HIV/AIDS, and the ongoing burden of HIV/AIDS among PWID, we are unaware of any studies that have explored the prevalence and correlates of PO injection among PWID living with HIV/AIDS.

Over the previous decade, many jurisdictions in North America and abroad have established treatment as prevention (TasP) initiatives to control the HIV/AIDS pandemic. The goal of TasP is to optimize HIV testing and access to highly-active antiretroviral therapy (HAART) to reduce individual-level HIV-1 plasma RNA viral loads (VLs) to below detectable levels in order to prevent progression to AIDS and premature death, and virtually eliminate onward HIV transmission. In order to achieve its goal, TasP-based strategies aim to scale-up engagement on HAART, especially among traditionally hard-to-treat HIV-positive groups such as PWID [15–17]. Although scale-up of HAART has led to dramatic declines in HIV/AIDS-associated morbidity and mortality among many groups worldwide [16, 18], a substantial proportion of PWID continues to encounter significant socio-structural barriers to HAART access and adherence (e.g., homelessness, incarceration) [19]. Vancouver, Canada offers a unique setting to study PO injection among HIV-positive PWID, as the availability of POs and the prevalence of PO injection grew substantially between the early 2000s, peaked around 2008, and remains relatively high [20]; meanwhile, extensive efforts are being made to seek, test, and treat PWID as part of a community-wide TasP campaign. This study was therefore undertaken to examine the prevalence and various social, structural, behavioral, and clinical-level correlates of PO injection among HIV-positive PWID in Vancouver, Canada within the context of a community-wide TasP initiative.

METHODS

Study Sample

The AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) is an ongoing open prospective observational study of HIV-positive adults who use illicit drugs in Vancouver, Canada. The cohort has been described in detail elsewhere [21, 22]. Briefly, participants are recruited through extensive street outreach and snowball sampling in Vancouver's Downtown Eastside (DTES) neighbourhood, the local epicenter of drug use and related harms including overdose and HIV/AIDS morbidity and mortality [23]. Individuals are eligible for ACCESS if they are HIV-positive, aged 18 years or older, reside in the

greater Vancouver region, have used an illicit drug other than cannabis in the previous month, and provide written informed consent. At baseline and semi-annually, participants complete a standardized interviewer-administered questionnaire eliciting socio-demographic, behavioral, and health-related information. Nurses collect blood samples for serologic analysis, and can provide basic medical care and referrals to external health care services. ACCESS participants receive a $30 (CAD) honorarium for each study visit. The University of British Columbia/Providence Health Care Research Ethics Board has provided ethical approval for the study.

As described in previous work [24, 25], the local setting includes a universal healthcare system offered at no cost to the patient, and a province-wide centralized free HIV/AIDS laboratory monitoring and antiretroviral therapy (ART) dispensation program. Through a confidential linkage to this laboratory and dispensary, the study accesses a complete longitudinal profile of all participant CD4 cell counts and plasma HIV-1 RNA viral load (VL) tests as well as records detailing each dispensation of antiretroviral agents, including regimen type and dosage.

Measures

The current study includes ACCESS participants who completed at least one interview between December 2005 and November 2013, and provided a blood sample for CD4 and HIV-1 RNA counts within 6 months of their baseline interview. Observations were further restricted to periods of active injection drug use for each participant (i.e., reporting injection drug use ≥1 time in the 6 months before an interview).

PO injection was assessed through the following question: “In the last 6 months, which of the following drugs did you inject?” to which participants were provided an extensive list and pictures of common POs. As new POs became available throughout the study period, the list was updated regularly to reflect current trends of PO use in the Vancouver area. The most recent follow-up questionnaire (November 2013) included oxycodone (‘OxyNeo’, ‘OxyContin’, ‘Percocet’), morphine, hydromorphone (‘Dilaudid’), meperidine (‘Demerol’), methadone, fentanyl, hydrocodone, and pentazocine (‘Talwin’). If required, participants could also identify any POs they had recently injected that were not specifically listed.

We considered various socio-demographic, social, structural, drug-related, and clinical explanatory variables as potential correlates of PO injection, including: age (per 10-year increase); gender (male vs. female); ethnicity (Caucasian vs. other); relationship status (married/common-law vs. single); highest level of education (≥secondary school vs. <secondary school); employment status (employed vs. unemployed); homelessness (yes vs. no); incarceration (yes vs. no); heroin injection (yes vs. no), cocaine injection (yes vs. no); crack smoking (yes vs. no); methadone maintenance treatment (yes vs. no); drug dealing (yes vs. no); and sex work (yes vs. no) With the exception of age, gender, ethnicity, and education, all variables refer to events or exposures in the 6-month period prior to the study interview. Finally, we examined the following HIV-related clinical characteristics measured at the time of each interview: recent (previous 6 months) engagement on ART (≥1 day dispensed vs. 0 days); CD4 cell count (per 100 cells/mL); and HIV-1 RNA viral load (using the Roche Amplicor Monitor Assay [Roche Molecular Systems, Mississauga, Canada])

Consistent with previous work [26], both CD4 and VL measures used all the observations available in the records of the clinical monitoring laboratory from tests conducted by the study, or by the participant's physician in the community. For both, we used the median value of all observations conducted in the 6 months prior to the study interview or, if none, the most recent observation (10.2 % of VL observations, 11.5 % of CD4 observations). To assess the possible relationship between PO injection and risk of onward transmission, we dichotomized the VL variable at 1500 c/mL [27].

Analysis

As a first step, we observed descriptive characteristics of study participants at baseline, and used Pearson's Chi square and Wilcoxon rank sum tests to compare categorical and continuous independent variables, respectively, among those who did and did not report injecting POs. We employed generalized estimating equations (GEEs) to model bivariable and multivariable associations between independent variables and PO injection at each follow-up period. This approach uses repeated measures to identify factors potentially associated with a time-updated binary outcome over an entire study period [28]. As participants may have injected POs during some biannual follow-up periods but not others, this model can estimate the within- and between-subject correlation of each characteristic with periods of PO injection and non-injection. GEEs use an exchangeable correlation structure to provide standard errors for each parameter, which are adjusted for multiple observations per person.

We started by examining the bivariable relationship between each independent variable and PO injection using a GEE model. To build an initial GEE multivariable model, we started with a set of variables comprising those that were significant at $p < 0.2$ in the bivariable analysis. We then removed covariates one-by-one, beginning with the covariate with the highest p value, and examined model quasi-information criterion (QIC) for each of these reduced models. The final multivariable model was chosen based on lowest QIC. Because of the correlation between ART exposure and HIV-1 plasma viral load, and as ART exposure is known to be on a causal pathway to viral load, we excluded viral load from the multivariable model building procedure. Data was analyzed using R (version 2.15.1, R Foundation for Statistical Computing, Vienna, Austria). All p-values are two-sided.

RESULTS

Between December 2005 and November 2013, 830 ACCESS participants were recruited and provided informed consent. Of these, 735 (88.6 %) had at least one CD4 and VL determination and were eligible for inclusion. Of these, 101 (13.7 %) participants did not report injecting drugs over the study period and were excluded from the analysis. After removing observations with missing values (n = 161; 4.6 %), the final analytical sample consisted of 634 PWID, including 210 (33.1 %) women, who contributed 3311 observations over a median of 4 (IQR: 2–8) study interviews. The ethnic composition of the sample was predominantly Caucasian (n = 364; 57.4 %), followed by Indigenous (n = 247; 39.0 %), Asian (n = 8; 1.26 %), Hispanic (n = 8; 1.26 %), and African ancestry (n = 7; 1.10 %). As displayed in Table 1, at baseline, the median age of participants was 42.9 (IQR: 36.6–48.3)

and 413 (65.1 %) received ≥1 day of ART in the previous 6 months. In the 6 months before their baseline interview, 171 (27.0 %) participants reported injecting POs (Table 1). Over the entire study period, the median prevalence of recent (i.e., past 6-month) PO injection was 24.2 % (IQR: 21.5–25.8 %).

Table 2 presents a summary of the bivariable and multivariable odds ratio estimates from the GEE models. As shown, Caucasian ethnicity, homelessness, incarceration, heroin injection, crack smoking, drug dealing and a VL >1500 c/mL were all positively associated with PO injection; while age, being on methadone maintenance and recent dispensation of ART were all negatively associated with periods of PO injection at the bivariable level ($p < 0.05$). Factors that remained associated with PO injection in the multivariable GEE model were age (adjusted odds ratio [AOR]: 0.96, 95 % confidence interval [CI]: 0.94–0.97), Caucasian ethnicity (AOR: 1.65, 95 % CI: 1.20–2.26), heroin injection (AOR: 2.23, 95 % CI: 1.84–2.70), methadone maintenance treatment (AOR: 0.76, 95 % CI: 0.62–0.93), and drug dealing (AOR: 1.88, 95 % CI: 1.56–2.25).

As a follow-up to the finding that ART dispensation was significantly and negatively associated with PO injection at the bivariable level but not at the multivariable level, we explored various two-term models using recent ART dispensation as a constant in each model in order to understand which factor(s) rendered this association statistically non-significant. In these sub-analyses, the association between ART dispensation and PO injection lost its significance in models with either heroin injection or age as the second term (data not shown).

DISCUSSION

In this study, the first to our knowledge to identify the prevalence and factors associated with PO injection among HIV-positive PWID, we observed a median one-quarter (24.2 %) of actively injecting participants reporting PO injection. While we could not identify any other prevalence estimates of PO injection among studies restricted to HIV-positive PWID, the current estimates are lower than those recorded in other studies of PWID (i.e., HIV-positive and HIV-negative). For example, approximately three-quarters of a Montreal sample of PWID reported injecting POs in the previous 6 months in 2009 [13]. The lower rate recorded in this study may be due to the relatively older age (median: 42.9) of our cohort, the high availability of heroin in our setting [20], and the implementation of provincial strategies designed to counter rising rates of inappropriate PO prescribing and non-medical PO use (e.g., a tightly regulated provincial opioid prescribing program [29], and a database of up-to-date PO dispensation records [30]). In line with previous research documenting higher rates of PO abuse and dependence among Caucasian individuals [31,32], PO injecting in this setting was associated with Caucasian ethnicity. We also identified independent associations between PO injection and other high-risk drug- and disease-related factors, including heroin injection, drug dealing, and not being on methadone maintenance treatment.

Periods of PO injection appear to be most prevalent alongside other high-risk substance use. For example, we found that the odds of injecting POs were more than double for people who inject heroin. This association was hypothesized to be strong at the study outset, considering

the psychoactive and physiological properties shared by both types of opioids, as well as previous qualitative research describing the frequent substitution of heroin with POs when heroin is not imminently available [33]. Numerous studies have also demonstrated the high frequency of heroin injection among PO-using PWID [10, 13,34–36], and the accompanying heightened risk for overdose associated with injecting both types of opioids [37]. The finding of an association with crack smoking in the unadjusted model adds to ethnographic research undertaken elsewhere in Canada demonstrating the high rate of PO injection among people who primarily smoke crack [38], and exemplifies a culture of poly-drug use involving both opioids and stimulants in the present setting. This type of poly-drug use is an ongoing concern, as it has been linked with a constellation of drug-related morbidity and mortality [39, 40]. We also observed a significant and negative association between periods of methadone maintenance therapy and periods of PO injection, which both demonstrates the potential for methadone to lower risky opioid use in this setting, and also highlights the importance of including people who inject POs in strategies to promote opioid substitution treatment (OST).

We also observed a strong and independent association between drug dealing and PO injection. While drug dealing among PWID has been previously linked with other intensive drug use, including daily heroin and cocaine injection [41], this study may be the first to consider drug dealing in relation to PO injection. The diversion of POs is unique from traditional drug-dealing pathways in that, except in a few cases of illicitly manufactured POs (e.g., illicit fentanyl powders [42]), POs are manufactured for medical purposes. Research into mechanisms of PO diversion demonstrates that most illicitly used POs originate in the medical system (e.g., obtained through a family or friend's prescription, “doctor shopping”, pharmacy theft, prescription forgery [32, 43]) rather than through unregulated and illegal manufacturing and importation methods common to other illicit drugs such as heroin. Considering these distinctions, the observed association between PO injection and drug dealing could be reflective of a group of PO-using PWID who may have been previously naïve to illicit drug dealing but gained an opportunity through novel dealing pathways exclusive to PO dealing (e.g., selling pills from one's prescription) that arose alongside the more recent establishment of a strong local illicit PO market [20]. A study of people who use illicit drugs in New York City found that roughly one-quarter of PO dealers sold POs exclusively [44], suggesting the absence of such dealers without the presence of POs on the illicit market. Furthermore, our study's consideration of HIV-positive PWID, rather than PWID in general, may have promoted the relationship with reporting selling drugs. For example, in qualitative work from Florida, dealers often reported HIV/AIDS patients as a reliable source of POs, as many of these individuals tended to have recurring prescriptions [45]. In order to fully understand the drivers of this association, follow-up research characterizing people who use POs and deal drugs in the current setting is required.

Previous research has demonstrated that among ART-exposed individuals living with HIV/AIDS, the non-medical use of POs may negatively influence ART adherence and—consequently—virologic outcomes. For example, a recent US study of HIV-positive indigent adults found that rates of ART adherence were significantly lower among those who met the criteria for PO misuse [46]. Rather than examining adherence, the current study considered exposure to ART in a setting with no financial barriers to treatment. In bivariable analyses,

we found that periods of PO injection were characterized by lower odds of engagement on HIV treatment and higher odds of having a VL >1500 c/mL. However, in a multivariable model that included recent ART dispensation among a number of other socio-demographic and behavioral vulnerabilities, we found no significant association between PO injection and the odds of receiving ≥1 day of ART in the previous 180 days. In sub-analyses, we found that the inclusion of age and heroin injection attenuated the relationship between PO injection and ART dispensation, suggesting that these factors accounted for the lower rate of ART engagement initially detected alongside periods of PO injection. However, as there is significant overlap between periods of PO injection and heroin injection, PO-using PWID may prove an important group for targeted strategies to promote ART initiation and improve adherence in the current efforts to seek, test, and treat hard-to-reach people living with HIV/AIDS.

The current study highlights concerns related to illicit PO use among PWID, but reveals areas for potential improvement, particularly in the context of the local TasP initiative. Ensuring that HIV-positive PWID, including those who inject POs, have access to ART and are able to reach optimal adherence is a critical step to improving disease outcomes both on an individual and population level [47, 48]. The finding of an inverse association between methadone maintenance treatment and PO injection highlights an important sub-group of drug users within the PWID population who may benefit from interventions to increase initiation into OST. Engagement in OST has shown widespread health benefits for PWID, including increasing the likelihood of ART uptake and adherence [49–51], and VL suppression [51, 52]. Therefore, there is an urgent need to address and reduce barriers to OST initiation and retention among HIV-positive PWID, including those who inject POs. As the local system of care is largely dominated by methadone, PO-using PWID may benefit from the expansion alternative OST options that have demonstrated success among patients who have previously not benefited from methadone (e.g., diacetylmorphine [53], buprenorphine [54], morphine [55]). As we continue to work towards the goal of preventing onward HIV transmission through treating hard-to-reach vulnerable groups, this research supports the notion that HIV treatment for PWID be part of a continuum of care built through the integration of, and partnerships with, primary care, mental health and addiction medicine, and social services [56].

Limitations

While extensive efforts (e.g., street outreach, snowball sampling) were made to recruit a representative sample of HIV-positive PWID, the non-random nature of our sample may not be fully generalizable to some PWID populations in Canada and elsewhere—particularly in regions with dissimilar sample ethnic demographics, as Caucasian ethnicity was associated with PO injection and is the predominant ethnic composition of our sample. Second, while we used linkage to clinical measures wherever possible (e.g., CD4 count, VL, ART dispensation), the self-reported nature of our outcome of interest (PO injection) and other behavioral covariates are vulnerable to recall and response biases; however, PWID self-report, including engagement in substance use, has been shown to be sufficiently reliable and valid [57]. Third, earlier versions of our questionnaire did not allow for the

measurement of pain for the first half of the study period. In order to maximize study power, we opted against including a pain correlate to allow for a longer study period.

CONCLUSIONS

In conclusion, periods of PO injection were common among HIV-positive PWID and associated with various socio-demographic and drug-related vulnerabilities. While Caucasian ethnicity, drug dealing, and heroin injection were significantly and positively associated with PO injection, older age and engagement in methadone maintenance therapy were significantly and negatively associated. An inverse bivariable association between engagement in ART and PO injection did not remain significant after controlling for a host of socio-demographic, behavioral, and clinical confounders. Particularly as work is underway to identify, treat, and retain as many HIV-positive PWID as possible, our findings highlight the critical need to develop comprehensive strategies addressing the interconnected health care needs of PWID, including addiction, HIV and its associated symptoms, chronic pain management, and other drug-related morbidity.

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Table 1

ACCESS sample characteristics at baseline, stratified by prescription opioid injection (n = 634)

Characteristic	PO injection		Odds ratio (95 % CI)	*p* value
	Yes 171 (27.0 %)	No 463 (73.0 %)		
Age[a] (median, IQR)	41 (35–47)	43 (38–49)	0.96 (0.95–0.99)	0.002
Gender				
Male	117 (68.4)	307 (66.3)	1.10 (0.76–1.60)	0.616
Female	54 (31.6)	156 (33.7)		
Ethnicity				
Caucasian	111 (64.9)	250 (54.0)	1.58 (1.10–2.27)	0.014
Other	60 (35.1)	213 (46.0)		
Relationship status[b]				
Partner	57 (33.3)	106 (22.9)	1.68 (1.15–2.47)	0.008
Single	114 (66.7)	357 (77.1)		
Education status				
≥Secondary	88 (51.5)	194 (41.9)	1.47 (1.03–2.09)	0.032
<Secondary	83 (48.5)	269 (58.1)		
Employed[b]				
Yes	28 (16.4)	83 (17.9)	0.90 (0.56–1.43)	0.648
No	143 (83.6)	380 (82.1)		
Homeless[b]				
Yes	63 (36.8)	130 (28.1)	1.49 (1.03–2.17)	0.033
No	108 (63.2)	333 (71.9)		
Incarcerated[b]				
Yes	39 (22.8)	57 (12.3)	2.10 (1.34–3.31)	0.001
No	132 (77.2)	406 (87.7)		
Heroin injection[b]				
Yes	142 (83.0)	212 (45.8)	5.80 (3.74–8.99)	<0.001
No	29 (17.0)	251 (54.2)		
Cocaine injection[b]				
Yes	105 (61.4)	274 (59.2)	1.10 (0.77–1.57)	0.612
No	66 (38.6)	189 (40.8)		
Crack smoking[b]				
Yes	145 (84.8)	370 (79.9)	1.40 (0.87–2.25)	0.162
No	26 (15.2)	93 (20.1)		
Syringe lending[b]				
Yes	8 (4.68)	7 (1.51)	3.20 (1.14–8.96)	0.020

Characteristic	PO injection		Odds ratio (95 % CI)	*p* value
	Yes 171 (27.0 %)	No 463 (73.0 %)		
No	163 (95.3)	456 (98.5)		
Methadone treatment[b]				
Yes	86 (50.3)	197 (42.5)	1.37 (0.96–1.94)	0.082
No	85 (49.7)	266 (57.5)		
Drug dealing[b]				
Yes	81 (47.4)	117 (25.3)	2.66 (1.85–3.84)	<0.001
No	90 (52.6)	346 (74.7)		
Sex work[b]				
Yes	25 (14.6)	71 (15.3)	0.95 (0.58–1.55)	0.824
No	146 (85.4)	392 (84.7)		
ART dispensation[b]				
≥1 day	105 (61.4)	308 (66.5)	0.80 (0.56–1.15)	0.230
0 days	66 (38.6)	155 (33.5)		
Viral load[b]				
>1500 c/mL	91 (54.5)	205 (44.3)	1.45 (1.02–2.06)	0.039
≤1500 c/mL	71 (46.5)	258 (55.7)		
CD4 cell count[a,b] Median (IQR)	3.2 (1.8–4.6)	3.1 (2.0–4.8)	0.97 (0.90–1.06)	0.534

Some columns may not add up to 100 % as participants may choose not to answer sensitive questions

95 % CI: 95 % confidence interval

[a] Wilcoxon rank sum test used for continuous variables

[b] Denotes events in the previous 6 months

Table 2

Bivariable and multivariable GEE analyses of factors associated with recent prescription opioid injection among 634 PWID

Characteristic	Unadjusted		Adjusted	
	Odds ratio (95 % CI)	*p*value	Odds ratio (95 % CI)	*p*value
Age				
Per 10 year increase	0.96 (0.94–0.97)	<0.001	0.97 (0.96–0.99)	0.003
Gender				
Male vs. female	1.18 (0.87–1.60)	0.283		
Ethnicity				
Caucasian vs. other	1.34 (1.00–1.79)	0.053	1.65 (1.20–2.26)	0.002
Relationship status[a]				
Partner vs. single	0.99 (0.80–1.23)	0.960		
Education status[a]				
≥Sec vs. <sec	1.11 (0.83–1.49)	0.486		
Employed[a]				
Yes vs. no	0.96 (0.78–1.17)	0.659		
Homeless[a]				
Yes vs. no	1.43 (1.17–1.76)	0.001	1.15 (0.95–1.40)	0.154
Incarcerated[a]				
Yes vs. no	1.36 (1.07–1.74)	0.012	1.06 (0.83–1.35)	0.635
Heroin injection[a]				
Yes vs. no	2.44 (1.91–3.13)	<0.001	2.23 (1.84–2.70)	<0.001
Cocaine injection[a]				
Yes vs. no	1.04 (0.83–1.29)	0.738		
Crack smoking[a]				
Yes vs. no	1.41 (1.10–1.79)	0.006	1.19 (0.96–1.48)	0.118
Syringe lending[a]				
Yes vs. no	1.71 (0.95–3.08)	0.073	1.38 (0.80–2.39)	0.249
Methadone treatment[a]				
Yes vs. no	0.76 (0.59–0.97)	0.031	0.76 (0.62–0.93)	0.009
Drug dealing[a]				
Yes vs. no	2.14 (1.74–2.63)	<0.001	1.88 (1.56–2.25)	<0.001
Sex work[a]				
Yes vs. no	1.35 (0.99–1.84)	0.059	1.07 (0.81–1.42)	0.631
ART dispensation[a]				

Characteristic	Unadjusted		Adjusted	
	Odds ratio (95 % CI)	*p*value	Odds ratio (95 % CI)	*p*value
≥1 vs. 0 days	0.73 (0.57–0.94)	0.014	1.02 (0.82–1.27)	0.834
Viral load[a]				
>1500 vs. ≤1500 c/mL	1.34 (1.06–1.69)	0.013	–	–
CD4 cell count[a] Per 100 cells/mL	0.95 (0.89–1.01)	0.097	0.97 (0.92–1.02)	0.266

GEE generalized estimating equation, *95 % CI* 95 % confidence interval, – indicates variable was excluded from multivariable model-building protocol

[a]Denotes events/exposures in the previous 6 months