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A Longitudinal Analysis of Daily Pill Burden and Likelihood of Optimal Adherence to Antiretroviral Therapy among People Living with HIV Who Use Drugs

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Abstract

Objectives—Among people living with HIV (PLWH), high levels of adherence to prescribed antiretroviral therapy (ART) is required to achieve optimal treatment outcomes. However, little is known about the effects of daily pill burden on adherence amongst PLWH who use drugs. We sought to investigate the association between daily pill burden and adherence to ART among members of this key population in Vancouver, Canada.

Methods—We used data from the ACCESS study, a long-running community-recruited cohort of PLWH who use illicit drugs linked to comprehensive HIV clinical records. The longitudinal relationship between daily pill burden and the odds of ≥95% adherence to ART among ART-exposed individuals was analyzed using multivariable generalized linear mixed-effects modelling, adjusting for sociodemographic, behavioral and structural factors linked to adherence.

Results—Between December 2005 to May 2014, the study enrolled 770 ART-exposed participants, including 257 (34%) women, with a median age of 43 years. At baseline, 437 (56.7%) participants achieved ≥95% adherence in the previous 180 days. Among all interview periods, the median adherence was 100% (inter-quartile range: 71%—100%). In a multivariable

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Competing interests

The authors have no conflicts of interest to disclose.

Authors' contributions

NA.MS wrote the manuscript, M-J.M designed the research and analyzed the data, L.R, T.K, J.S, J.M and A.K provided insight and expertise related to the field.

model, a greater number of pills per day was negatively associated with ≥95% adherence (Adjusted Odds Ratio [AOR] = 0.87 per pill, 95% Confidence Interval [95% CI]: 0.84–0.91). Further analysis showed that once-a-day ART regimens were positively associated with optimal adherence (AOR = 1.39, 95% CI: 1.07 – 1.80).

Conclusions—In conclusion, simpler dosing demands (i.e., fewer pills and once-a-day single tablet regimens) promoted optimal adherence among PLWH who use drugs. Our findings highlight the need for simpler dosing to be encouraged explicitly for PWUD with multiple adherence barriers.

Introduction

The widespread scale-up of access to antiretroviral therapy (ART) has resulted in substantial declines in rates of morbidity and mortality among people living with HIV (PLWH) (Abdool Karim et al., 2010). However, treatment success is largely determined by the level of adherence achieved by individuals, which in turn strongly predicts virologic and immunologic responses. Fortunately, optimal adherence to ART typically leads to suppression of plasma HIV-1 RNA viral load (VL), eliminating the risk of onward viral transmission (Montaner et al., 2014) and stalling progression to AIDS (Thompson et al., 2012).

Incomplete adherence to antiretroviral therapy (ART) among people who use illicit drugs (PWUD) continues to pose a serious challenge to achieving optimal clinical outcomes (Altice et al., 2010). Studies have identified several risk factors for non-adherence to ART among members of this key population, largely focused around considerations related to psychoactive drug use, including inability to access addiction treatment (Palepu et al., 2004), as well as other social and structural factors. For example, socioeconomic obstacles, such as low income (Wood et al., 2002; Bouhnik et al. 2002), and living in unstable housing or being homeless, have been shown to limit engagement in HIV care. (Evans et al., 2006) Further, criminalization and incarceration of PWUD has been associated with interruption of ART in many settings (Milloy et al., 2011), and the social stigmatization of PWUD and PLWH creates additional barriers to uptake and maintenance of ongoing care (Ahern et al., 2007).

In contrast to behavioral, social and structural factors, less well detailed is the extent to which the complexity of medication regimens affect the ability of PWUD to achieve optimal adherence to ART (Stone et al., 2004). Among non-drug using people living with HIV, observational studies of pill burden have identified the role of simplified antiretroviral regimens on improved adherence (Stone et al., 2001; Buscher et al., 2012; Bangsberg et al., 2010). Two meta-analysis identified an advantage of once-daily dosing using studies that assessed adherence through methods including pill counts and medication event monitoring systems (Parienti et al., 2009; Nachega et al., 2014). Additionally, single pill fixed-dose regimens have been associated with improved adherence (Sax et al., 2012). In contrast, several studies relying on self-reported adherence have not found an association between pill burden and adherence (Hernández Arroyo et al., 2015; Gianotti et al., 2013).

Although studies among non-drug-using groups of individuals on ART have revealed the importance of medication-related factors on adherence (Gallant et al., 2006; Portsmouth et

al. 2005), very few studies have investigated the effect of factors such as daily pill burden and dosing frequency on adherence among PWUD (Spire et al., 2007). Such studies are needed to inform treatment guidelines and guide efforts to provide optimal care among this key population. Further, studies examining pill burden and dosing frequency among non-drug using people living with HIV have predominantly used cross-sectional designs and relied on self-reported measures of adherence. The current analyses uses data gathered via a long-running community-recruited longitudinal cohort of PLWH who use drugs with complete pharmacy dispensation data. Using those data, we assessed the potential impact of daily pill burden on adherence to ART within British Columbia, Canada, where all medically eligible persons living with HIV have access to free ART.

Methods

In this study, we used data from the AIDS Care Cohort to Evaluate Exposure to Survival Services (ACCESS), an ongoing prospective observational cohort of HIV-seropositive PWUD in Vancouver, Canada. As described in detail elsewhere (Milloy et al., 2011; Strathdee et al., 1998), study recruitment began in 2005 centered on the Downtown Eastside neighbourhood, an area characterized by an open drug market with high prevalence of injection and non-injection drug use, HIV infection and poverty (Tyndall et al., 2003). Eligibility criteria include being HIV seropositive, aged >18 years, use of illicit drugs (other than or in addition to cannabis) in the month prior to enrollment, and the provision of written informed consent. At the baseline interview and each semi-annual interview thereafter, participants answer an interview-administered questionnaire, are examined by a study nurse, and provide blood for serologic analyses. The ACCESS study has been approved by the University of British Columbia/Providence Health Care Research Ethics Board.

Information on sociodemographic characteristics, illicit drug use and other key activities and exposures collected at each interview is augmented with data on HIV treatment and clinical monitoring available from the British Columbia Centre for Excellence in HIV/AIDS. As described in detail elsewhere (Wood et al., 2008), data from this province-wide centralized ART pharmacy provides comprehensive information on all ART dispensation, including antiretroviral agent dispensed, dose and date dispensed to all participants throughout the study period, including clinical and community settings and during periods of incarceration. This information is confidentially linked to participants by using their personal health number (PHN), a unique and persistent identifier issued for medical billing and tracking purposes to all residents of British Columbia. The Centre's HIV/AIDS monitoring lab also provides a complete retrospective and prospective clinical profile for each participant. Of note, all medical care including HIV medications is provided at no cost to residents of British Columbia, allowing us to examine determinants of medication adherence independent of the influence of cost.

The present analysis included all those participants who were ART-exposed at the time of recruitment or who initiated ART following study recruitment. In addition, participants were included if they completed ≥ 1 study interview following ART initiation and had ≥ 1 CD4 observation within 180 days of the earliest eligible interview. For all participants meeting these criteria, all observations following ART initiation were included.

In these analyses, the outcome of interest was adherence to ART in the 180-day period prior to the study interview. Consistent with previous analyses (Milloy et al., 2011; Lappalainen et al., 2015), adherence was calculated as the number of days for which ART was dispensed in the last 180 days from pharmacy records over the number of days since the participant had started ART, to a maximum of 180 days, dichotomized at 95%. We have previously shown that optimal adherence using pharmacy refill data is strongly associated with both virologic suppression and survival (Wood et al., 2004; Wood et al., 2003).

Our primary explanatory variable of interest was pill burden, or the daily number of pills prescribed to be ingested per day, expressed as a continuous measure. Using the pharmacy dispensation data, we ascertained the pill burden on the date of the interview. If the individual was not dispensed ART for that day, we used the pill burden on the most recent dispensation. In a sub-analysis, we repeated analyses using a dichotomized measure of being on a single-tablet regimen (STR; i.e., 1 pill vs. > 1 pill per day).

In analyses we considered a range of explanatory variables that could confound the relationship between pill burden and adherence including: age (per year older); gender (male vs. non-male); ancestry (white vs. non-white); unstable housing (yes vs. no); participation in addiction treatment (yes vs. no); illicit income generation (yes vs. no); formal employment (yes vs. no); injection drug use (yes vs. no); alcohol use (< 4 drinks/day vs. ≥ 4 drinks/day); binge drug use, defined as any period of uncontrolled or higher than usual frequency of drug use (yes vs. no); and incarceration (yes vs. no). A clinical variable, CD4+ cell count (per 100 cells/mL) was included in the analysis to account for HIV disease progression. As in previous analyses, we used the mean of all CD4 cell count observations conducted within the previous 180 days at each interview or, if none were available, the most recent observation. All non-fixed variables were time-updated and referred to the period starting 180 days prior to the interview, except for age, which referred to current status.

As a first step, we examined the distribution of explanatory characteristics at the earliest study interview, in addition to recent adherence (≥ 95 vs. <95%), stratified by daily pill burden (dichotomized at the median of all observations, or >4 vs. ≤4 pills/day). Next, we estimated univariate statistics for the relationships between adherence and all explanatory variables over the study period using generalized linear-mixed effects modelling. This method accounts for the correlation inherent in serial measures from the same individual and across individuals at the same time point, and can estimate the independent effect of the explanatory variable of interest on adherence. To prepare a multivariable model, we used an *a priori*-defined modelling procedure. First, we fit a full model including all explanatory variables. Using a manual backward approach, we constructed reduced models, eliminating one variable from the full set of explanatory variables one at a time. The coefficient values from the full model and each of the reduced models were compared. We continued this process until the maximum change from the full model exceeded 5%. This procedure retains secondary covariates with greater relative influence on the relationship between the outcome and the primary explanatory variable. The same technique has been used in previous analyses to successfully estimate the relationship between the outcome of interest and primary explanatory variable (Lima et al., 2009; Milloy et al., 2011).

Results

Between December, 2005 and May, 2014, 845 eligible individuals were identified, of whom 770 (91%) were ART-exposed and had complete baseline CD4 and VL data. Study participants included 257 (34%) women, with a median age of 43 years (inter-quartile range: 37–48), and contributed 5810 interviews over the course of the study period, equal to 2905 person-years of observations. Of these, 3465 (59.6%) were characterized by ≥95% adherence in the previous 180 days.

Selected sociodemographic and clinical characteristics as well as levels of adherence, stratified by median daily pill burden (i.e., > 4 vs. ≤ 4 pills/day) for this analytic sample are presented in Table 1. Of note, at baseline, participants who were prescribed 4 pills per day or less showed higher levels of optimal adherence to ART (62%) compared to those prescribed greater than 4 pills per day (47%), reflecting an odds ratio [OR] of 0.54 (95% confidence interval [95% CI]: 0.40–0.72.)

Crude and adjusted longitudinal estimates of the odds of optimal adherence for the primary variable (daily dosage of pills) and other secondary variables are presented in Table 2. In univariable analyses, a greater daily dosage of pills was negatively associated with achieving ≥95% adherence (Odds Ratio [OR] = 0.85 per pill, 95% CI: 0.81 – 0.88.) In a multivariable model, a greater daily dosage of pills remained negatively associated with achieving ≥95% adherence (Adjusted Odds Ratio [AOR] = 0.87 per pill, 95% CI: 0.84–0.91), after adjusting for confounders including age, ancestry, being engaged in addiction treatment, ≥ daily heroin injection, year of observation, and alcohol use. Table 3 presents crude and adjusted longitudinal estimates for the secondary analysis of the odds of optimal adherence for once-a-day single tablet regimens (STR) versus regimens with more pills per day. In an adjusted model, individuals prescribed once-a-day STR regimens were 39% more likely to achieve optimal adherence than individual on non-STR once-a-day regimens (AOR = 1.39, 95% CI: 1.07 – 1.80), after adjustment for alcohol use and binge drug use.

Discussion

In this longitudinal study investigating the relationship between daily pill burden and adherence to ART among PLWH who use drugs in Vancouver, Canada, our results demonstrate that a greater number of pills prescribed per day was independently associated with a lower likelihood of achieving optimal adherence to ART. In a secondary multivariable analysis, use of once-a-day single-tablet regimens was associated with higher rates of optimal adherence to ART.

Previous studies that have examined the role of pill burden on adherence levels among individuals receiving ART have shown mixed results (Stone et al., 2001; Buscher et al., 2012; Bangsberg et al., 2010; Parienti et al., 2009; Nachega et al., 2014; Sax et al., 2012; Hernández Arroyo et al., 2015; Gianotti et al., 2013). Inconsistencies are potentially explained by the different methods used to assess adherence. Nevertheless, previous findings consistent and inconsistent with the current study's results have been limited by the lack of consideration of substance use and PWUD in analyses, as well as consideration of a range of

potential confounders in the HIV pandemic. Given potentially important considerations for PWUD in relation to achieving ART adherence (Palepu et al., 2004), including significant social and structural barriers to accessing and sustaining optimal HIV care, previous studies may therefore not be generalized to PWUD (Airoldi et al., 2010)

Despite current availability of Single Tablet Regimen (STR) offering simple regimens to PLWHA in order to promote adherence when taking medication, remarkably little work has been done to assess the potential importance of medication-related factors among diverse key affected populations. PWUD are a population that could particularly benefit advances in ART medication, and the current study provides critical evidence to inform treatment guidelines and efforts to scale up ART among PWUD to support optimal outcomes among this population. Our findings point to the possibility of improving ART adherence using simplified or single-tablet ART regimens. In our secondary analyses, we observed that the effect of STR regimens on optimal adherence was independent of patterns of both binge drug use and alcohol use, suggesting that scaling up access to once-a-day regimens could mitigate the well-described negative impact of substance use on suboptimal HIV treatment outcomes (Altice et al., 2010). Our findings support the need of promoting STR-based regimens for individuals facing multiple barriers to optimal adherence, such as PWUD, as a part of initiatives to scale-up access and adherence to ART.

Few studies have examined adherence to ART and dosing requirements in the context of illicit drug use. In one qualitative study involving people using injection and non-injection drugs, participants reported that irregular lifestyles caused difficulty accommodating their ART regimen into their schedules, particularly when prescribed thrice-a-day dosing (Witteveen E, 2002). Treatment adherence is further complicated by the lack of consideration by physicians of an individual's behavioral and social conditions by prescribing complex regimens (Osterberg et al., 2005). A prospective cohort study evaluating ART adherence among HIV-infected individuals with alcohol and other substance use issues showed that use of drugs or alcohol in the previous 30 days was associated with poorer adherence (Palepu et al., 2004). As essential as it is to promote treatment for substance use disorders among HIV-infected individuals with persistent drug and alcohol use, it is also important for ART regimen decisions to be tailored to patients' daily activities and exposures by reducing regimen complexity as much as possible.

The problem of pill burden in the management of HIV treatment for PWUD is extended in the presence of other co-morbidities including viral hepatitis, tuberculosis and mental illness (Kamarulzaman and Altice, 2015). Among those who inject drugs, co-infection of HIV and hepatitis C (HCV) global prevalence is estimated at 82.4%, which accounts for more than half of the 2.3 million people who are HIV-HCV infected worldwide (Platt et al. 2016). The risk of disease progression into advanced stages is even higher among individuals with HIV-HCV co-infections, making the coordination of HCV treatment as important as HIV management (Sulkowski, 2001). PWUD is also at high risk of contracting tuberculosis due to increased risk for incarceration where such settings are prone to poor ventilation and overcrowding (Getahun et al., 2012). Failure to adhere to ART is also associated with interrupted depression treatment or untreated mental illness; a condition that is common among individuals with substance use problems (Buckingham et al., 2013). In summary, co-

treatment of HIV, viral hepatitis, tuberculosis and mental illness contribute to the overall pill burden of HIV-positive PWUD, therefore it is imperative to apply STR in managing HIV treatment to reduce this burden.

A range of studies have investigated the impact of adherence interventions on improved treatment outcomes among HIV-positive PWUD (Binford et al., 2012). For example, the implementation of directly administered ART (DAART) through observed ingestion of ART medication at clinical settings has been shown to improve adherence among PWUD, however, the same effects were not sustained once DAART was discontinued (Berg et al., 2011). Overall, such intervention does not only result in short term outcomes but can also be costly for countries with limited resources (Ford et al., 2013). In view of this evidence, the benefits of medication simplification in improving treatment outcomes among PWUD deserve closer attention in addition to existing adherence interventions. This research has several limitations to note. First, while our cohort was recruited using community-based methods, we cannot conclude it is necessarily representative of PLWH who use drugs in our setting or others. Second, several explanatory variables such as injection and binge drug use, alcohol consumption and incarceration were derived from participant self-report. Social desirability bias might generate under-reporting of these stigmatized exposures. However, our outcome of interest was ascertained through administrative data and we do not believe individuals differentially self-reported explanatory variables based on adherence or pill burden. Finally, adherence measurement based on dispensation data from the pharmacy does not necessarily ensure consumption of the medications. Nevertheless, we emphasize that this method of measuring adherence has been shown to predict virologic response and mortality. (Wood et al., 2004; Wood et al., 2003).

Conclusions

In conclusion, our results demonstrate that a greater number of ART pills per day was negatively associated with the likelihood of achieving optimal medication adherence and that use of once-a-day single-tablet regimens was associated with higher rates of optimal adherence to ART among PWUD living with HIV/AIDS in a setting of universal no-cost healthcare. These results suggest that minimizing pill burden and promoting regimen simplicity (ie. STR) should be prioritized within the context of ART programs for PWUD. Although complex regimens are often required for patients with long treatment histories and extensive comorbidities, the findings from our study suggests that patients with more demanding regimens (in terms of pill burden or dosing frequency) require additional support to achieve optimal adherence. Given the challenges that many HIV-positive PWUD face in adhering to their medication in many settings worldwide, strategies that are effective in increasing medication simplification and managing complex regimens could contribute to ongoing efforts to scale-up ART to eliminate HIV-associated morbidity, mortality and viral transmission.

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Table 1

Baseline characteristics of 770 PLWHA who use illicit drugs stratified by daily pill burden (> 4 pills/day vs. ≤ 4) in Vancouver, Canada

Characteristic	Pill burden ≤ 4 46 (%) n = 389	Pill burden > 4 54 (%) n = 456	Odds Ratio (95% CI)	*p* - value
ART adherence				
< 95%	185 (37.7)	148 (53.0)	1.00	
≥ 95%	306 (62.3)	131 (47.0)	0.54 (0.40–0.72)	< 0.001
Age				
Per year older	44.0 (37.5–48.5)	43.6 (37.7–48.7)	0.99 (0.98–1.02)	0.959
Gender				
Male	326 (66.4)	187 (67.0)	1.00	
Non-male	165 (33.6)	92 (33.0)	0.97 (0.71–1.33)	0.873
Ancestry				
Non-white	206 (42.0)	121 (43.3)	1.00	
White	285 (58.0)	158 (56.7)	0.94 (0.70–1.27)	0.705
Unstable housing				
No	155 (31.6)	105 (37.6)	1.00	
Yes	336 (68.4)	174 (62.3)	0.76 (0.56–1.04)	0.096
Addiction treatment				
No	228 (46.4)	127 (45.5)	1.00	
Yes	263 (53.6)	152 (54.5)	1.04 (77.3–1.39)	0.821
Illicit income				
Generation				
Yes	343 (69.9)	179 (64.2)	1.00	
No	148 (30.1)	100 (35.8)	1.29 (0.95–1.77)	0.109
Employment				
No	408 (83.1)	234 (83.9)	1.00	
Yes	83 (16.9)	45 (16.1)	0.95 (0.64–1.41)	0.840
Injection heroin				
< Daily	430 (87.8)	245 (88.1)	1.00	
≥ Daily	60 (12.2)	33 (11.9)	0.97 (0.61–1.52)	0.909
Injection cocaine				
< Daily	454 (92.7)	258 (92.8)	1.00	
≥ Daily	36 (7.3)	20 (7.2)	0.98 (0.55–1.72)	0.999
Crack smoking				
< Daily	326 (66.4)	196 (70.3)	1.00	
≥ Daily	165 (33.6)	83 (29.7)	0.84 (0.61–1.15	0.297
Cannabis use				
< Daily	375 (76.4)	216 (77.4)	1.00	
≥ Daily	116 (23.6)	63 (22.6)	0.94 (0.66–1.34)	0.790

Characteristic	Pill burden ≤ 4 46 (%) n = 389	Pill burden > 4 54 (%) n = 456	Odds Ratio (95% CI)	*p* - value
Alcohol use				
< 4 drinks/day	370 (75.4)	215 (77.1)	1.00	
≥ 4 drinks/day	121 (24.6)	64 (22.9)	0.91 (0.64–1.29)	0.661
Binge drug use				
No	271 (55.2)	166 (59.5)	1.00	
Yes	220 (44.8)	113 (40.5)	0.84 (0.62–1.13)	0.257
Incarceration				
No	434 (88.4)	253 (90.7)	1.00	
Yes	57 (11.6)	26 (9.3)	0.78 (0.48–1.28)	0.397
CD4 cell count				
Per 100 cells/mL	3.3 (2.1–4.6)	2.8 (1.5–4.2)	0.63 (0.47–0.85	0.002
Year of observation				
Per year later	2009 (2007–2011)	2007 (2006–2009)	0.62 (0.57–0.67)	< 0.001

Table 2

Longitudinal generalized linear mixed-effects analysis of adherence to ART among 770 PLWHA who use illicit drugs in Vancouver, Canada

	Unadjusted		Adjusted	
Characteristic	**Odds Ratio (95% CI)**	***p* - value**	**Odds Ratio (95% CI)**	***p* - value**
Pill burden[1]				
Per pill	0.85 (0.81 – 0.88)	< 0.001	0.87 (0.84–0.91)	< 0.001
Age[1]				
Per year	1.07 (1.05 – 1.08)	< 0.001	1.05 (1.04–1.07)	< 0.001
Gender				
(Non-male vs. male)	0.65 (0.49 – 0.86)	0.002		
Ancestry				
(white vs. non-white)	1.61 (1.23 – 2.11)	0.001	1.39 (1.06–1.81)	0.015
Unstable housing[2]				
(yes vs. no)	0.89 (0.75 – 1.05)	0.175		
Addiction treatment				
(yes vs. no)	1.55 (1.29 – 1.86)	< 0.001	1.50 (1.25–1.80)	< 0.001
Illicit income generation[2]				
(yes vs. no)	0.62 (0.51 – 0.74)	< 0.001		
Employment[2]				
(yes vs. no)	0.98 (0.80 – 1.19)	0.817		
Injection heroin use				
(<Daily vs ≥Daily)	0.47 (0.36–0.62)	< 0.001	0.52 (0.40–0.68)	< 0.001
Crack smoking				
(<Daily vs. ≥Daily)	0.52 (0.43–0.62)	< 0.001		
Cocaine injection				
(<Daily vs. ≥Daily)	0.68 (0.51–0.90)	0.007		
Cannabis use				
(<Daily vs. ≥Daily)	0.94 (0.76–1.15)	0.549		
Alcohol use[2]				
(yes vs. no)	0.75 (0.63 – 0.90)	0.002	0.81 (0.67–0.97)	0.026
Binge drug use[2]				
(yes vs. no)	0.71 (0.62 – 0.82)	< 0.001		
Incarceration[2]				
(yes vs. no)	0.70 (0.52 – 0.92)	0.013		
CD4[2]				
per 100 cells	1.30 (1.24 – 1.36)	< 0.001		
Year of observation				
Per year later	1.13 (1.12–1.13)	< 0.001	1.03 (1.03–1.03)	< 0.001

[1]Variables based on current status

[2]Variables that are time-updated referring to the last 6 months from the last interview

Table 3

Longitudinal generalized linear mixed-effects analysis of adherence to ART among 770 PLWHA who use illicit drugs in Vancouver, Canada, with the primary explanatory variable: Once vs. ≥ once/day

	Unadjusted		Adjusted	
Characteristic	**Odds Ratio (95% CI)**	***p* - value**	**Odds Ratio (95% CI)**	***p* - value**
Pill burden[1]				
Once vs. ≥ once/day	1.43 (1.10 – 1.85)	0.007	1.39 (1.07–1.80)	0.013
Age[1]				
Per year	1.07 (1.05 – 1.08)	<0.001		
Gender				
(non-male vs. male)	0.65 (0.49 – 0.86)	0.002		
Ancestry				
(white vs. non-white)	1.61 (1.23 – 2.11)	0.001		
Unstable housing[2]				
(yes vs. no)	0.89 (0.75 – 1.05)	0.175		
Addiction treatment				
(yes vs. no)	1.55 (1.29 – 1.86)	<0.001		
Illicit income generation				
(yes vs. no)	0.62 (0.51 – 0.74)	<0.001		
Employment[2]				
(yes vs. no)	0.98 (0.80 – 1.19)	0.817		
Heroin injection				
(≥Daily vs. <daily)	0.47 (0.36–0.62)	< 0.001	0.49 (0.38–0.65)	< 0.001
Crack smoking				
(≥Daily vs. <daily)	0.52 (0.43–0.62)	< 0.001		
Cocaine injection				
(≥Daily vs. <daily)	0.68 (0.51–0.90)	< 0.001		
Cannabis use				
(≥Daily vs. <daily)	0.94 (0.76–1.15)	0.549		
Alcohol use[2]				
(yes vs. no)	0.75 (0.63 – 0.90)	0.002	0.77 (0.64–0.92)	0.004
Binge drug use[2]				
(yes vs. no)	0.71 (0.62 – 0.82)	<0.001		
Incarceration[2]				
(yes vs. no)	0.70 (0.52 – 0.92)	0.013		
CD4[2]				
per 100 cells	1.30 (1.24 – 1.36)	<0.001	1.29 (1.23–1.35)	< 0.001
Year of observation				
Per year	1.13 (1.12–1.13)	< 0.001		

[1] Variables based on current status

[2]Variables that are time-updated referring to the last 6 months from the last interview