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INJECTION DRUG USE AND HIV ANTIRETROVIRAL THERAPY DISCONTINUATION IN A CANADIAN SETTING

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Abstract

We investigated whether drug-related behaviors predicted antiretroviral therapy (ART) discontinuation among a cohort of injection drug users (IDU) in a Canadian setting. Cox regression analyses were used to investigate the impact of drug use patterns on rates of ART discontinuation among a sample of HIV-positive IDU in Vancouver, Canada between May 1996 and April 2008. In total, 408 HIV-positive IDU initiated ART during the study period, among whom 257 (63.0%) discontinued ART at least once. Rates of ART discontinuation were not significantly elevated among those who reported ongoing injection of heroin, cocaine, or other illicit drugs in comparison to those who reported not injecting drugs. However, public drug use was significantly predictive of ART discontinuation. Our findings may contribute to a reconsideration of the role of active drug use in determining retention in ART programs among IDU.

Keywords

Antiretroviral therapy ART Injection drug use Retention Discontinuation HIV

INTRODUCTION

In most large urban areas around the world, injection drug use has been implicated in the transmission of HIV [1]. Outside of Africa, at least one-third of all new HIV infections are among individuals who use injection drugs (IDU), while in some countries this rate is much higher [2]. In some settings, IDU constitute the primary population at risk of HIV infection. In the Russian Federation, for example, surveillance estimates suggest that the HIV prevalence among the country's approximately 1.9 million Russian IDU is over 35% [1].

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Similarly, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 60% of all HIV infections in Ukraine are among IDU [3]. In an effort to address the critical role that injection drug use has played in driving HIV transmission in all global regions, clinicians and policy makers have recommended a comprehensive package including harm reduction interventions, addiction treatment, and antiretroviral therapy (ART) targeted towards HIV-positive injection drug-using populations. This public health approach to tackling the health and social harms of injection drug use has been endorsed by the World Health Organization, UNAIDS, and the United Nations Office on Drugs and Crime (UNODC) [4], and draws its design from a large scientific evidence base [5, 6].

Strategies to “seek, test, treat and retain” vulnerable HIV-positive populations in ART have become increasingly prioritized as key to reducing health and social harms associated with HIV/AIDS [7]. While these strategies have demonstrated promise in reducing HIV transmission, however, limited data exist to guide optimal strategies to retain IDU on ART [8]. A key concern among clinicians is the potential that an aggressive rollout of ART among IDU populations, as suggested by UNAIDS [9], may result in suboptimal retention in treatment and a subsequent proliferation of ART resistance, especially among individuals who continue to inject drugs after enrolment in ART [10–14]. Since ART discontinuation is associated with the development of ART resistance and HIV disease progression [15], we sought to investigate the impact of ongoing injection drug use on rates of ART discontinuation among a cohort of HIV-positive IDU in Vancouver, Canada.

METHODS

The AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS) is an ongoing prospective cohort of HIV-positive drug users based in Vancouver, Canada, which has been described in detail previously [16]. Beginning in May 1996, the study began enrolling drug users who resided in the Greater Vancouver region in order to investigate drug-related health outcomes including HIV disease progression as well as barriers to health care access among this population, which resides in a Canadian province that provides ART free of charge to all clinically eligible individuals [17, 18]. ACCESS participants were recruited through street outreach and self-referral, and all participants provided written informed consent. At baseline and at scheduled semi-annual follow-up visits (i.e., every 6 months), study participants completed an interviewer-administered questionnaire and provided blood samples for disease monitoring. Participants were reimbursed \$20 for each visit and, when appropriate, were referred to additional health care, including addiction treatment [19]. Importantly, a data linkage with British Columbia’s province wide ART dispensation database allowed for the ascertainment of ART initiation dates and subsequent cessation events. Ethical approval for this study has been granted by the University of British Columbia/Providence Health Care Ethics Review Board.

The ACCESS questionnaire solicits detailed demographic data, as well as data on drug use patterns and related exposures. For the present investigation, our outcome of interest was ART discontinuation. Consistent with past analyses [20], ART discontinuation was defined based on pharmacy dispensation records indicating that a participant did not pick up any ART for 90 days or longer after the end of the prescription refill date. Because of the

province wide ART dispensation data linkage, all ART prescription refills were recorded regardless of whether study participants used the same or different pharmacies throughout the study period.

Since we were interested in the impact of different patterns of drug injecting, the primary independent variable of interest examined the role of exclusive heroin or cocaine injection, combined heroin and cocaine injection (i.e., speedball), or injecting other drugs in the past 6 months. Included in the “other drugs” category was injection of crystal methamphetamine, methadone, morphine, talwin and ritalin, dilaudid, or ketamine (all refer to illicit or non-prescribed use). The reference category for this variable was no report of injection drug use in the past 6 months.

Individuals were eligible for the present analysis either if they reported being on ART at the time of recruitment or if they subsequently enrolled and used ART during the study period. We first generated descriptive statistics and univariate analyses to assess the incidence of ART discontinuation and predictors of discontinuation. We were aware that confounding might have persisted if the rate of discontinuation differed between participants enrolled in ART at varying stages of disease progression, or among those who participated in higher risk behaviors or who were potentially at higher risk of ART discontinuation as a result of sociodemographic differences. Therefore, we constructed a recurrent events Cox regression analysis that included drug-related and clinical independent variables potentially predictive of ART discontinuation [21]. Aside from the injection drug use patterns described above, potential sociodemographic and drug-related predictors of ART discontinuation that we included in this model were: age, gender, Aboriginal ancestry (yes vs. other), area of residence (defined as residing in Vancouver’s downtown eastside, the local epicenter of the drug-related HIV outbreak vs. other areas), enrolment in addiction treatment, public drug use, and binge drug use. Public drug use was defined as having consumed injection or non-injection drugs in a public location (i.e., park, bathroom, alley, etc.) in the previous 6 months. Binge drug use was defined as an episode during which drugs were consumed at a higher frequency than normal in the previous 6 months.

All drug-related and behavioral variables refer to behaviors in the past 6 months, and were time-updated based on data from the semi-annual follow-up visits. We also considered the following clinical variables: continuously distributed measures of baseline CD4 cell count (cells/ μ L, per 100-cell increase) and baseline plasma HIV-1 RNA (log10/ μ L, per log 10 increase), physician experience, and year of baseline interview (per year increase). In line with a previous analysis in our setting, we defined an HIV-experienced physician as one who had previously enrolled six or more individuals into the HIV treatment registry at the time the participant initiated treatment [22]. Because participants were continuously enrolled in the treatment program during the study period, a ‘non-experienced’ physician can become ‘experienced’ over time. However, the experience level assigned to each participant was fixed, based on the HIV-related experience of the physician at the time of each participant’s first study follow-up interview.

All behavioral variables were lagged in our analyses in order to protect against reverse causality. Specifically, we employed measures of our time-updated independent variables of

interest in our model from interviews that occurred prior to ART discontinuation. We also opted a priori to include the primary independent variable of interest (i.e., injection drug use patterns), as well as baseline CD4 cell count, plasma HIV-1 RNA, and physician experience in the multivariate model regardless of their significance in univariate analysis. This was done to ensure that we adjusted for the potential contribution of clinical status to ART discontinuation. All statistical analyses were conducted using SAS 9.2 (SAS, Cary, NC, USA). All P values are two-sided, and the analyses were undertaken using an a priori design in which a significant association was defined at the $P < 0.05$ level.

RESULTS

Between May 1996 and April 2008, 408 HIV-positive IDU enrolled in ART participated in this study, including 164 (40.2%) female participants and 150 (36.8%) participants reporting Aboriginal ancestry. The median age of participants at baseline was 39 (Interquartile range: 33–45). Participants contributed 1,932 observations over the study period, and 526 ART discontinuation events were observed among 257 (63.0%) participants for a cumulative incidence of 70.6% (95% CI: 65.8–75.3%). The median number of discontinuation events per participant was 1.3 (Inter-quartile Range: 0–2.0). With respect to participant retention, 67.4% of sample participants reported at least one follow-up visit and the median follow-up duration was 25 months (interquartile range: 10–74). Of the 526 discontinuation events observed, 49 (9.3%) occurred among participants reporting injecting heroin, 133 (25.3%) occurred among participants injecting cocaine, 201 (38.2%) occurred among participants injecting heroin and cocaine, 7 (1.3%) occurred among participants injecting drugs other than heroin and/or cocaine, and 136 (25.9%) occurred among participants that were not injecting drugs.

Descriptive statistics and univariate analyses of factors associated with discontinuation are presented in Table 1. As is shown, compared to reporting no injection drug use, only reporting injection of both heroin and cocaine injection in combination was predictive of ART discontinuation in unadjusted analyses [Hazard Ratio (HR) = 1.40, 95% Confidence Interval (CI): 1.08–1.81, $P = 0.011$]. In terms of other potential drug-related predictors of ART discontinuation, public drug use (HR = 2.28, 95% CI: 1.79–2.91, $P < 0.001$) was also predictive of ART discontinuation.

Table 2 provides the adjusted hazard ratios for ART discontinuation by type of drug use. As described, after adjustment for baseline CD4 cell count and plasma HIV-1 RNA load and other potential confounders found to be significant in univariate analysis, there were no significant differences in risk of ART discontinuation between those participants that reported no injection drug use and those that reported injection drug use, including heroin injection [Adjusted Hazard Ratio (AHR) = 1.19, 95% CI: 0.85–1.68, $P = 0.307$], cocaine injection (AHR = 1.14, 95% CI: 0.88–1.47, $P = 0.317$), both heroin and cocaine injection (AHR = 1.16, 95% CI: 0.91–1.46, $P = 0.231$), or injection of other drugs (AHR = 0.79, 95% CI: 0.36–1.70, $P = 0.539$). With respect to other variables, reporting public drug use (AHR = 1.67, 95% CI: 1.31–2.13, $P < 0.001$) and female gender (AHR = 1.23, 95% CI: 1.03–1.46, $P = 0.023$) were associated with an increased risk of ART discontinuation, while older age at

baseline (AHR = 0.97, 95% CI: 0.96–0.98, $P < 0.001$) and later enrolment in the study (AHR = 0.92, 95% CI: 0.88–0.95, $P < 0.001$) were protective against ART discontinuation.

CONCLUSIONS

Over a 12-year period, pharmacy records indicate that almost two-thirds of a cohort of HIV-positive illicit drug users had at least one ART discontinuation episode. However, in a multivariate recurrent events Cox regression model, and despite adjustment for a variety of potential confounders, patterns of injection drug use were not predictive of ART discontinuation in comparison to abstinence from drug injecting.

While our results will need to be confirmed through further research, these findings are consistent with a previous meta-analysis that found no significant differences in the development of ART-resistant HIV among individuals with and without a history of injection drug use [23]. Together, these suggest that clinicians should not make decisions on whether to initiate eligible HIV-positive individuals in ART based solely on abstinence from drug injecting. Rather, in accordance with recently revised therapeutic guidelines from major medical and HIV policy organizations [24, 25], and in light of efforts to increase ART initiation and retention among marginalized populations such as IDU [8, 9], decisions to enroll eligible individuals on ART should be done on a case by case basis. In all cases, however, care should be taken to ensure high levels of ART regimen adherence among individuals that may be at particularly high risk of non-compliance [25]. To that end, recent research into the integration of opioid substitution treatment, including methadone and buprenorphine maintenance treatment, into HIV primary care, suggests potential ways to increase ART retention among IDU [26]. However, it is noteworthy that enrolment in addiction treatment was not significantly protective against ART discontinuation in our analysis, though this likely reflects the elevated frequency of cocaine use in our study setting, a drug for which no effective substitution treatment is currently recommended [27]. It is also of note that we observed a significantly increased risk of ART discontinuation among individuals injecting speedballs (i.e., heroin and cocaine in combination) in univariate analysis but not in multivariate analysis. This nevertheless highlights the potential negative effects of poly substance use on ART discontinuation.

Finally, injecting in public has previously been implicated in a variety of negative health outcomes [28–30], and was also the only significant drug-related predictor of ART discontinuation in our multivariate analysis. Critically, those IDU that inject in public environments have been shown to be at increased risk of HIV transmission through syringe sharing [29], tissue infections through rushed injection practices [31–33], and are more likely to engage in unsafe disposal of used injecting equipment [34]. The independent association between public drug use and ART discontinuation observed herein likely reflects the risky nature of public drug use, and reaffirms the need for structural interventions to address the health needs of this vulnerable population [29, 35].

This study has limitations. First, cohort participants were not randomly recruited and therefore the results presented may not be representative of the broader population of HIV-positive IDU in Vancouver. Second, while participant reports of discontinuation of ART and

clinical status were confirmed through a data linkage with a local HIV treatment registry, we relied on self-report for the behavioral and drug-related variables included in our analyses. Given that drug use and related behaviors are highly stigmatized, these activities may have been underreported by participants. Despite this potential for bias, we know of no reason why cohort participants who did and did not discontinue ART would differentially report on their drug use. Finally, there may be unmeasured variables that are important for determining ART discontinuation, including measures of mental illness, which were not routinely evaluated as part of this study.

In the present study, we observed no significant differences in rates of ART discontinuation among participants that reported injecting drugs and those that reported becoming abstinent from injecting. While adherence and ART retention interventions should nevertheless be targeted towards active drug users, these findings may contribute to a reconsideration of the role of active drug use in clinical decision-making surrounding ART initiation.

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Table 1

Univariate predictors of antiretroviral therapy discontinuation among injection drug users in Vancouver, 1996–2008 ($n = 408$)

Characteristic	Discontinued antiretroviral therapy*		Unadjusted hazard ratio (95% CI)	P-value
	No N = 1,406 n (%)	Yes N = 526 n (%)		
Injection drug use				
No injection drug use	461 (32.8)	136 (25.9)	1.00	–
Heroin only	132 (9.4)	49 (9.3)	1.10 (0.75–1.60)	0.644
Cocaine only	358 (25.5)	133 (25.3)	1.10 (0.84–1.44)	0.482
Heroin and cocaine	423 (30.1)	201 (38.2)	1.40 (1.08–1.81)	0.011
Other drugs	32 (2.3)	7 (1.3)	0.56 (0.27–1.16)	0.118
Binge drug use				
No	1,118 (79.5)	383 (72.8)		
Yes	288 (20.5)	143 (27.2)	1.00 (0.82–1.23)	0.991
Public drug use				
No	1,311 (93.2)	427 (81.2)		
Yes	95 (6.8)	99 (18.8)	2.28 (1.79–2.91)	<0.001
Overdose				
No	1,327 (94.4)	487 (92.6)		
Yes	79 (5.6)	39 (7.4)	1.32 (0.95–1.84)	0.104
DTES residence				
No	573 (40.8)	253 (48.1)		
Yes	833 (59.2)	273 (51.9)	0.83 (0.67–1.01)	0.066
Homeless				
No	1,247 (88.7)	435 (82.7)		
Yes	159 (11.3)	91 (17.3)	1.44 (1.12–1.87)	0.005
Aboriginal ancestry				
No	872 (62.0)	321 (61.0)		
Yes	534 (38.0)	205 (39.0)	1.16 (0.91–1.46)	0.229
Gender				
Male	836 (59.5)	278 (52.9)		
Female	570 (40.5)	248 (47.1)	1.31 (1.04–1.64)	0.021
Baseline age				
Median (IQR)	37.8 (32.7–43.3)	34.9 (28.4–41.1)	0.95 (0.94–0.97)	<0.001
Year of enrolment				
Median (IQR)	1998 (1997–2000)	1998 (1997–2000)	0.89 (0.86–0.92)	<0.001
Addiction treatment				
No	509 (36.2)	204 (38.7)		

Characteristic	Discontinued antiretroviral therapy*		Unadjusted hazard ratio (95% CI)	P-value
	No N = 1,406 n (%)	Yes N = 526 n (%)		
Yes	897 (63.8)	322 (61.2)	0.92 (0.75–1.12)	0.667
Physician experience				
Enrolled <5 HIV patients	1,142 (81.2)	421 (80.2)		
Enrolled ≥5 HIV patients	264 (18.8)	104 (19.8)	0.98 (0.75–1.29)	0.905
Baseline CD4 count (copies/ μL)				
Median (IQR)	2.20 (1.30–3.73)	2.50 (1.70–3.80)	1.03 (0.98–1.07)	0.228
Baseline viral load (log₁₀/μL)				
Median (IQR)	11.26 (10.21–12.25)	11.24 (10.13–12.04)	1.11 (1.06–1.16)	<0.001

* Frequencies represent the number of events throughout the study period rather than number of participants

CI Confidence interval, DTES downtown eastside, IQR interquartile range

Table 2

Adjusted hazard ratios of HIV antiretroviral discontinuation for types of drug use ($n = 408$)

	Adjusted hazard ratio	(95% CI)	P-value
Type of drug use			
No injection drug use	1.00	–	–
Heroin only	1.19	(0.85–1.68)	0.307
Cocaine only	1.14	(0.88–1.47)	0.317
Heroin and cocaine	1.16	(0.91–1.46)	0.231
Other drugs	0.79	(0.36–1.70)	0.539
Gender			
Female versus male	1.23	(1.03–1.46)	0.023
Baseline age			
Per year older	0.97	(0.96–0.98)	<0.001
Year of study enrolment			
Per year later	0.92	(0.88–0.95)	<0.001
Baseline CD4 count (copies/ μ L)	1.02	(0.98–1.06)	0.370
Baseline HIV viral load (copies/ μ L)	1.04	(1.00–1.09)	0.062
Physician experience			
Enrolled <5 versus 5 patients	0.95	(0.76–1.18)	0.616
Public drug use			
Yes versus no	1.67	(1.31–2.13)	<0.001
Homelessness			
Yes versus no	1.19	(0.93–1.52)	0.167

The number of observations for each drug use category can be derived from Table 1

CI Confidence interval, DTES downtown eastside