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ORIGINAL PAPER

Prevalence and Correlates of Reporting Difficulty Taking Antiretroviral Treatment Among HIV-Positive Illicit Drug Users in Vancouver, Canada: A Longitudinal Analysis

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Abstract

People living with HIV who use illicit drugs continue to experience high rates of suboptimal treatment outcomes from antiretroviral therapy (ART). Although previous studies have identified important behavioural, social and structural barriers to ART adherence, the effects of patient-level factors have not been fully evaluated. Thus, we sought to investigate the prevalence and correlates of reporting ART was difficult to take among a cohort of illicit drug users in Vancouver, Canada. We accessed data from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing prospective cohort of HIV-positive illicit drug users linked to comprehensive HIV clinical monitoring records. We used generalized linear mixed-effects modeling to identify factors longitudinally associated with periods in which individuals reported they found ART difficult to take. Between December 2005 and May 2014, 746 ART-exposed illicit drug users were recruited and contributed at least one study interview. Finding ART hard to take was reported by 209 (28.0%) participants at baseline, and 460 (61.7%) participants throughout the study period. Patients ingesting a greater daily pill count (adjusted odds ratio [AOR] = 1.12 per pill, 95% confidence interval [CI] 1.08–1.17) and experiencing barriers to healthcare (AOR = 1.64, 95% CI 1.34–2.01) were more likely to report difficulty taking ART. Patients less likely to report satisfaction with their HIV physician (AOR = 0.76, 95% CI 0.58–1.00) and achieve a non-detectable HIV viral load (AOR = 0.62, 95% CI 0.51–0.74) were more likely to report finding ART hard to take. In this community-recruited cohort of ART-exposed illicit drug users, a substantial proportion reported they found HIV treatment hard to take, which was clearly linked to higher dissatisfaction with healthcare experiences and, most importantly, a lower likelihood of experiencing optimal virologic outcomes. Our findings reveal a number of opportunities to improve HIV treatment experiences and outcomes for people who use illicit drugs, including the use of treatment regimens with lower pill burdens, as well as reducing barriers to healthcare access.

Keywords ART · HIV-positive · Illicit drug users · Canada · Antiretroviral treatment · Antiretroviral therapy

Introduction

Globally, rates of HIV/AIDS-related morbidity and mortality have declined substantially as a result of the introduction of combination antiretroviral therapy (ART) [1–3]. However, optimal ART adherence (i.e., ≥95% adherence) remains a critical component for the achievement of viral suppression in order to stall HIV disease progression and prevent onward viral transmission [4–7].

Although the therapeutic effects of ART have been robustly demonstrated, substantial heterogeneity has been observed across the different key populations of people living with HIV. Among HIV-infected people who use illicit drugs (PWUD), rates of ART uptake are low, even where

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ART is freely available [8–10], and treatment outcomes are frequently suboptimal [10–12]. Further, antiretroviral therapy is often initiated at later disease stages [10, 13], despite strong evidence demonstrating early initiation as a predictor of improved individual- and community-related outcomes [14–16]. Fortunately, with adequate adherence to treatment, PWUDs can achieve parity with non-drug users in rates of optimal treatment outcomes [17, 18]. Thus, there is an urgent need to fully evaluate the factors associated with optimal ART adherence among PWUDs [19].

Important individual-level barriers to ART adherence among PWUDs include ongoing illicit drug use, low self-regulatory efficacy, expectations of negative outcomes [20], and fear of HIV status disclosure [21]. Physiological side effects, particularly adverse gastrointestinal events, are also common reasons for ART discontinuation [14, 22]. Though a number of patient-level barriers to uptake and engagement in ART have been identified among PWUDs, the experience of taking ART has not been fully investigated. Therefore, this study sought to longitudinally investigate the prevalence and correlates of self-reporting ART was difficult to take among a cohort of illicit drug users in Vancouver, Canada.

Methods

For this study, we used data from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing longitudinal prospective cohort study of HIV-positive illicit drug users in Vancouver, Canada. Beginning in December 2005, study participants were recruited through extensive street outreach in Vancouver's Downtown Eastside (DTES) neighborhood, an urban area marked by high levels of poverty, illicit drug use, and incidence of HIV-infection among injection drug users [23–25]. Eligibility for ACCESS is restricted to HIV-positive individuals aged ≥ 18 years with a history of illicit drug use (other than or in addition to cannabis) in the previous month, who have provided written informed consent. Study participants respond to an interviewer-administered questionnaire and, during an examination by a nurse, provide serum samples for serological analysis at baseline and at every 6-month follow-up. The structured interview collects comprehensive demographic data, along with descriptions of drug use and various related exposures. All survey respondents are remunerated $30 (CAD) at each interview. Our institutional Research Ethics Board provides ethics approval annually.

The information collected in the semi-annual ACCESS questionnaire is supplemented with HIV treatment and clinical outcome data from the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) Drug Treatment Program [26]. Information from this province-wide, centralized ART dispensary provides records on all antiretroviral drug dispensations for every study participant during the study period, as well as clinical information, including CD4+ cell counts and plasma HIV-1 RNA levels (measured by Amplicor Monitor Assay, Roche Molecular Systems, Mississauga, Canada). All HIV-positive residents of the province are eligible for no-cost HIV/AIDS treatment and care through the Medical Services Plan (MSP) of British Columbia, the province's publicly-funded health care system.

This study included all interview periods from individuals who were ART-exposed at baseline, or individuals who initiated ART treatment during follow-up. All interviews conducted after the earliest date of antiretroviral treatment dispensation were included. We further restricted our analytic sample to participants with ≥ 1 CD4+ count and ≥ 1 plasma HIV-1 RNA viral load (VL) within 6 months of their baseline interview.

For this analysis, the primary outcome of interest was self-reported difficulty taking ART, as assessed during the examination by the study nurse. We also included explanatory factors such as: age (at baseline); time since HIV diagnosis (in years); gender (male vs. non-male); ancestry (Caucasian vs. non-Caucasian); homelessness (yes vs. no); relationship status (legally married/common law/partner vs. other); formal employment (yes vs. no); education (≥ high school completion vs. < high school); injection drug use (yes vs. no); heavy alcohol use (≥ 4 drinks/day vs. < 4 drinks/day); comorbidity with severe depression, as measured by the Center for Epidemiologic Studies-Depression score [27], dichotomized at 16 (yes vs. no); participation in a methadone program (yes vs. no); satisfaction with healthcare provider (yes vs. no); and understanding how to take prescribed HIV medication (yes vs. no). The behavioural and drug use variables applied to a period of 6 months prior to the interview. Formal employment was defined as having a regular job, temporary job, or self-employment in the previous 6 months. Individuals with no fixed residence, or living on the streets at the time of the interview were classified as homeless. Heavy alcohol use referred to an average of ≥ 4 drinks per day within the past 6 months.

From the comprehensive HIV clinical monitoring and treatment dispensation records, we estimated ART pill burden, HIV MD experience, ART adherence and plasma VL. Using ART dispensation records, we defined pill burden as the maximum number of pills per dose for the most recent regimen dispensed. As in previous analyses [28], we defined an HIV physician as experienced if they had previously initiated more than six individuals on ART at the time the participant was first dispensed ART, as reflected by pharmacy records. We have found HIV experience to be independently associated with a greater likelihood of viral suppression [29]. To estimate ART adherence for each 180 day observation day period, we divided the number of days for which ART had been dispensed by the number of days since the

individual had initiated ART, to a maximum of 180 days. We dichotomized the proportion at ≥95 versus <95%. We have previously demonstrated this validated measure of adherence based on pharmacy refill data is associated with VL suppression and survival [30]. For VL, we used the median of all observations conducted in the 180 day period prior to each study interview, dichotomized at <50 versus ≥50 copies/mL. If none, we defined the period as characterized by detectable VL (i.e., ≥50 copies/mL) unless pharmacy records indicated more than 170 days of ART had been dispensed, as in a previous analysis [28].

Using this data, we first analyzed characteristics of the analytic sample at their earliest study interview, stratified by reporting they found treatment difficult to take. We compared the distribution of each explanatory variable in these strata through Wilcoxon rank sum tests (for continuous measures) and χ^2 tests (for categorical variables.) Next, we used generalized linear mixed-effects logistic regression to estimate the longitudinal relationship between reporting ART was difficult to take and each explanatory variable, accounting for the correlation inherent in repeated measures observed from individuals over time. To fit the multivariable model, we used a backwards selection procedure, beginning with all variables at $p < 0.1$ in bivariable analyses. Using an examination of each model's Akaike Information Criterion, we fit reduced models. Analyses were conducted using SAS 9.4 (Cary, NC); the threshold for statistical significance was set at $p < 0.05$. All p-values were two-sided.

Results

Between December 2005 and May 2014, a total of 746 individuals were recruited, completed ≥1 interviews, had complete HIV clinical data within ±180 days of the baseline interview and were included in these analyses. Of these respondents, 209 (28.0%) self-reported difficulty taking ART at the baseline interview. Among 5607 survey observations, 1180 (21.1%) included a report of finding treatment hard to take. Over the study period, 460 (61.7%) respondents reported difficulty taking treatment.

As presented in Table 1, 429 (57.5%) individuals achieved optimal ART adherence in the 180-day period prior to the baseline interview, and 314 (42.1%) individuals had an HIV-1 RNA viral load of <50 copies/mL plasma. Of note, 559 (74.9%) individuals reported injecting drug use in the last 6 months, and 585 (78.4%) individuals were noted for non-injection crack use. Concerning treatment-related characteristics, 220 (29.5%) respondents reported not always understanding how to take their HIV medication and 187 (25.1%) individuals experienced barriers to accessing healthcare services.

The bivariable and multivariable analyses are presented in Table 2. In the multivariable model, reporting ART was difficult to take was positively associated with receiving a high school diploma or greater (adjusted odds ratio [AOR] = 1.38; 95% confidence interval [CI] 1.08–1.77); reporting experiencing barriers to accessing healthcare (AOR = 1.65; 95% CI 1.34–2.02), and a greater daily pill count (AOR = 1.12 per pill increase; 95% CI 1.08–1.17). Reporting ART was difficult to take was negatively associated with male gender (adjusted odds ratio [AOR] = 0.73; 95% CI 0.56–0.96), reporting being satisfied with their doctor/clinic (AOR = 0.76; 95% CI 0.58–1.00), and exhibiting a non-detectable viral load (AOR = 0.62; 95% CI 0.51–0.74).

Discussion

In this investigation, we found that finding ART difficult to take was common, reported in approximately 20% of all interviews, and by a majority of participants at least once. Patients with a detectable viral load and less satisfaction with their healthcare providers were more likely to report difficulty taking ART. Patients experiencing healthcare barriers and ingesting a greater daily pill counts were also more likely to find ART hard to take. These data identify opportunities to improve HIV treatment and care for PWUDs in the context of the urgent need to scale up optimal access and adherence to ART.

Our findings suggest a number of potential avenues to ameliorate treatment-related experiences and outcomes. Firstly, past literature has indicated that lower pill burden (single-pill vs. multiple-pill regimens) and once-daily dosing frequency regimens (vs. twice-daily regimens) are associated with a higher likelihood of achieving optimal ART adherence and better virological suppression among non-drug-using samples of people living with HIV [31–33]. Contemporary ART regimen simplification strategies have reduced pill burdens for eligible HIV-positive individuals, improving treatment adherence and clinical outcomes [19, 34, 35]. Early evaluations of long-acting injectable nanoformulations of rilpivirine and GSK1265744 indicate a possibility of monthly treatment regimens [36]. Although simple treatment schedules have demonstrated their merit, individual adherence patterns are subject to a range of behavioural and physiological factors; thus, efforts to improve ART adherence must extend beyond regimen simplification [31, 37, 38].

Secondly, consistent with our observations, patient satisfaction with their healthcare provider (physician or clinic) was previously found to be an independent predictor of improved ART adherence [39]. Stigma and discrimination towards HIV and illicit drug use, is among many factors that fuel the negative relationship between patients and

Table 1 Baseline characteristics of 746 antiretroviral therapy-exposed people who use illicit drugs stratified by self-reported difficulty taking ART in Vancouver, Canada

Characteristic	Treatment is hard to take Yes n = 209	Treatment is hard to take No n = 537	Odds ratio (95% CI)	*p* value
Optimal ART adherence (≥ 95%)				
Yes	100 (47.8)	329 (61.3)	0.58 (0.42–0.80)	< 0.001
No	109 (52.2)	208 (38.7)		
Age				
Per year older	42.8 (36.3–49.1)	43.6 (37.2–48.4)	1.00 (0.98–1.02)	0.866
Gender				
Male	127 (60.8)	373 (69.5)	0.68 (0.49–0.95)	
Non-male	82 (39.2)	164 (30.5)		0.023
Ancestry				
Caucasian	112 (53.6)	296 (55.1)	0.94 (0.68–1.30)	0.706
Non-Caucasian	97 (46.4)	241 (44.9)		
Homeless				
Yes	59 (28.2)	138 (25.7)	1.14 (0.80–1.63)	0.476
No	149 (71.3)	397 (73.9)		
Methadone program				
Yes	105 (50.2)	235 (43.8)	1.29 (0.93–1.78)	0.122
No	103 (49.3)	297 (55.3)		
Education				
≥ High school completion	103 (49.3)	239 (44.5)	1.17 (0.85–1.61)	0.348
< High school completion	103 (49.3)	279 (52.0)		
Formal employment				
Yes	34 (16.3)	89 (16.6)	0.98 (0.63–1.51)	0.920
No	175 (83.7)	448 (83.4)		
Relationship				
Legally married/common law/partner	79 (37.8)	131 (24.4)	1.90 (1.34–2.67)	< 0.001
Other	125 (59.8)	393 (73.2)		
Injection drug use				
Yes	164 (78.5)	395 (73.6)	1.30 (0.89–1.91)	0.176
No	45 (21.5)	141 (26.3)		
Alcohol use				
≥ 4 drinks/day	13 (6.2)	15 (2.8)	2.31 (1.08–4.94)	0.027
< 4 drinks/day	196 (93.8)	522 (97.2)		
Viral load				
< 50 copies/mL	70 (33.5)	244 (45.4)	0.60 (0.43–0.84)	0.003
≥ 50 copies/mL	139 (66.5)	293 (54.6)		
Depression comorbidity				
Yes	116 (55.5)	274 (51.0)	1.36 (0.94–1.98)	0.104
No	54 (25.8)	174 (32.4)		
Healthcare barriers				
Yes	71 (34.0)	116 (21.6)	1.87 (1.31–2.66)	< 0.001
No	138 (66.0)	421 (78.4)		
Healthcare provider satisfaction				
Yes	180 (86.1)	485 (90.3)	0.64 (0.39–1.04)	0.071
No	29 (13.9)	50 (9.3)		
Medication understanding				
Yes	123 (58.9)	391 (72.8)	0.50 (0.36–0.70)	< 0.001
No	85 (40.7)	135 (25.1)		

Table 1 (continued)

Characteristic	Treatment is hard to take Yes n = 209	Treatment is hard to take No n = 537	Odds ratio (95% CI)	*p* value
Experienced healthcare provider				
≥ 6 HIV patients	169 (80.9)	413 (76.9)	1.09 (0.64–1.86)	0.748
< 6 HIV patients	21 (10.0)	56 (10.4)		
Time since diagnosis				
Per year	9.7 (5.3–12.9)	9.0 (4.6–12.7)	1.01 (0.99–1.04)	0.333
Maximum number of pills per dose	3.0 (2.0–5.0)	3.0 (2.0–5.0)	1.05 (0.99–1.10)	0.104

healthcare providers [40]. This, in addition to the lack of trust for providers, has a detrimental impact on patient satisfaction, which in turn results in poor treatment outcomes [41]. ART-exposed patients who faced institutional barriers such as long clinic wait times or averse experiences with clinic staff reported discouragement and reluctance to attend appointments regularly [42]. Studies have shown that limited access to health care is also attributed to social and economic disadvantages exhibited by members of this key population such as unstable housing [43] and limited employment opportunities [44]. Our findings highlight health system-level barriers that may underlie poor ART adherence and call for targeted solutions within the health sector, especially for HIV-positive PWUDs who typically contend with a variety of individual, social, and structural barriers to achieving optimal adherence. Further, we identified a link between non-male gender and a greater likelihood of finding ART difficult to take. It is possible that our current results might explain, in part, findings from previous analyses linking non-male gender with poorer antiretroviral medication adherence among PWUD [28, 45], a finding also demonstrated among other populations living with HIV. Thus, efforts to mitigate gendered barriers to ART, such as women-only health clinics and services, could be a means of supporting adherence and improving HIV treatment outcomes.

Our findings have relevance to both clinical practice and public policy. Specifically, renewed efforts are underway in many settings to promote HIV testing and scale-up access and adherence to ART in order to reduce individual and community-level HIV VL. Our finding of a link between finding ART difficult to take and VL detectability suggests a potential opportunity to improve rates of VL non-detectability through more tolerable ART formulations, and more welcoming clinical environments for HIV-positive PWUDs, particularly women.

The findings of our study have several limitations. First, the self-reported nature of some variables may limit the validity of our conclusions. However, the ACCESS questionnaire is structured to minimize response biases, encourage truthful answers, and reduce misinterpretation of survey questions. Rapport between interviewers and participants is well-established, and all interviews are conducted in a safe environment. Second, the recruited cohort is not a random sample, and thus, may not be representative of the whole population of HIV-positive illicit drug users in Vancouver, Canada or elsewhere.

In conclusion, in this study, one of the first to identify key demographic prevalence and correlates of difficulty taking ART among HIV-positive PWUDs, we found several factors implicated in finding ART difficult to take. Taken together, our data suggest several opportunities to inform new treatment initiatives to improve HIV- health outcomes for seropositive illicit drug users.

Table 2 Longitudinal generalized linear mixed-effects analysis of adherence to ART among 746 antiretroviral therapy-exposed people who use illicit drugs in Vancouver, Canada

Characteristic	Unadjusted		Adjusted	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age				
Per year	1.00 (0.99–1.02)	0.883		
Gender				
Male versus non-male	0.73 (0.56–0.96)	0.022	0.74 (0.57–0.96)	0.024
Ancestry				
Caucasian versus non-Caucasian	0.96 (0.75–1.24)	0.747		
Homeless				
Yes versus no	1.01 (0.80–1.27)	0.961		
Relationship status				
Legally married/common law/partner versus other	1.17 (0.95–1.43)	0.135		
Formal employment				
Yes versus no	0.93 (0.75–1.17)	0.539		
Education				
≥ High school completion versus < high school	1.40 (1.09–1.80)	0.009	1.38 (1.08–1.77)	0.011
Injection drug use				
Yes versus no	1.24 (1.03–1.50)	0.026		
Alcohol use				
≥ 4 drinks/day versus < 4 drinks/day	1.37 (0.87–2.16)	0.173		
Depression comorbidity				
Yes versus no	1.19 (0.93–1.54)	0.173		
Methadone program participation				
Yes versus no	0.95 (0.77–1.18)	0.632		
Viral load				
< 50 copies/mL versus ≥ 50 copies/mL	0.57 (0.48–0.68)	< 0.001	0.62 (0.51–0.74)	< 0.001
Time since diagnosis				
Per year	1.01 (0.99–1.03)	0.200		
Barriers to healthcare				
Yes versus no	1.71 (1.41–2.08)	< 0.001	1.65 (1.34–2.02)	< 0.001
Healthcare provider satisfaction				
Yes versus no	0.68 (0.52–0.88)	0.003	0.76 (0.58–1.00)	0.049
Medication understanding				
Yes versus no	0.69 (0.56–0.85)	< 0.001	0.82 (0.66–1.03)	0.089
Experienced healthcare provider				
≥ 6 HIV patients versus < 6 HIV patients	1.05 (0.77–1.43)	0.749		
Maximum number of pills per dose				
Per pill	1.10 (1.06–1.15)	< 0.001	1.12 (1.08–1.17)	< 0.001

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Compliance with Ethical Standards

Conflict of interest Dr. Milloy is supported in part by the US National Institutes of Health (R01-DA021525), a Scholar Award from the Michael Smith Foundation for Health Research and a New Investigator Award from the Canadian Institutes of Health Research. His institution has received an unstructured gift from NG Biomed Ltd. to support his research. Dr. Montaner is supported by the British Columbia Ministry of Health and through an Avant-Garde Award (No. 1DP1DA026182) from the National Institute of Drug Abuse, at the US National Institutes of Health. He has also received financial support from the International AIDS Society, United Nations AIDS Program, World Health Organization, National Institutes of Health Research-Office of AIDS Research, National Institute of Allergy & Infectious Diseases, The United States President's Emergency Plan for AIDS Relief (PEPfAR), UNICEF, the University of British Columbia, Simon Fraser University, Providence Health Care and Vancouver Coastal Health Authority. Dr. Socias is supported by a Michael Smith Foundation for Health Research (MSFHR) post-doctoral fellowship award and a Canada Addiction Medicine Research Fellowship from NIDA at the NIH (R25-DA037756). All other authors declare no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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