Published in final edited form as:
AIDS Behav. 2015 January ; 19(1): 120–127. doi:10.1007/s10461-014-0847-3.

High-intensity cannabis use and adherence to antiretroviral therapy among people who use illicit drugs in a Canadian setting

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Abstract

Background—Cannabis is increasingly prescribed clinically and utilized by people living with HIV/AIDS (PLWHA) to address symptoms of HIV disease and to manage side effects of antiretroviral therapy (ART). In light of concerns about the possibly deleterious effect of psychoactive drug use on adherence to ART, we sought to determine the relationship between high-intensity cannabis use and adherence to ART among a community-recruited cohort of HIV-positive illicit drug users.

Methods—We used data from the ACCESS study, an ongoing prospective cohort study of HIV-seropositive illicit drug users linked to comprehensive ART dispensation records in a setting of universal no-cost HIV care. We estimated the relationship between at least daily cannabis use in the last six months, measured longitudinally, and the likelihood of optimal adherence to ART during the same period, using a multivariate linear mixed-effects model accounting for relevant socio-demographic, behavioral, clinical and structural factors.

Results—From May 2005 to May 2012, 523 HIV-positive illicit drug users were recruited and contributed 2430 interviews. At baseline, 121 (23.1%) participants reported at least daily cannabis use. In bivariate and multivariate analyses we did not observe an association between using cannabis at least daily and optimal adherence to prescribed HAART (Adjusted Odds Ratio = 1.12, 95% Confidence Interval [95% CI]: 0.76 – 1.64, p-value = 0.555.)

Conclusions—High-intensity cannabis use was not associated with adherence to ART. These findings suggest cannabis may be utilized by PLWHA for medicinal and recreational purposes without compromising effective adherence to ART.

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Introduction

Since the introduction of antiretroviral therapy (ART), people living with HIV/AIDS (PLWHA) have experienced significant improvements in HIV-related morbidity and mortality (Lewden et al., 2012; Obel et al. 2011). Optimal adherence to ART has been shown to be strongly associated with virological suppression of plasma HIV-1 RNA viral load (pVL) and restoration of immunologic function (Cescan et al., 2011; May et al., 2006). However, despite these advances in HIV treatment, people who use illicit drugs (PWID) have frequently been found to exhibit sub-optimal adherence to ART and HIV/AIDS-related morbidity and mortality remains high in this population (Malta et al., 2008; Zwahlen et al., 2009; Larsen et al., 2010).

Among PLWHA, high-levels of sub-optimal adherence has been associated with ongoing active illicit drug use (Arnsten et al., 2002; Crisp et al., 2004; Hinklin et al., 2007; Lucas et al., 2001; Malta et al., 2008; Nolan et al., 2011; Palepu et al., 2006; Sharpe et al., 2004). Also, demographic characteristics and individual-level barriers to adherence among PWID include: age; female gender; alcohol use; lower self-efficacy; and psychiatric co-morbidities (Arnsten et al., 2007; Bouhnik et al., 2005; Carrieri et al., 2003; Hadland et al., 2012; Kerr et al., 2004; Tapp et al., 2011). Social and structural barriers to effective adherence, including homelessness and incarceration, have also been identified amongst drug users (Milloy et al., 2011; Milloy et al., 2012; Palepu et al., 2004; Palepu et al., 2011). Despite the risks active psychoactive drug use can pose for nonadherence to ART, few studies have evaluated the relationship of cannabis use on adherence to HIV treatment.

Cannabis is used frequently by PLWHA, with one observational study reporting 59% of PLWHA engaged in cannabis use in the past six months (Fogarty et al., 2007). PLWHA use cannabis to manage a number of HIV-related symptoms including anorexia, stress, nausea/vomiting, and pain (Prentiss et al., 2004; Ware et al., 2003; Woolridge et al., 2005). Despite the evidence to support the efficacy of cannabis in the amelioration of HIV-related symptoms (Abrams et al., 2003; Abrams et al., 2007; Ellis et al., 2009; Haney et al., 2007), the evidence regarding cannabis use and its possible impact on adherence is limited and we know of no long-term prospective studies assessing cannabis use as a factor that may affect adherence. Therefore, we conducted the present study to investigate the role cannabis use among a cohort of PWID living with HIV/AIDS in a setting with universal healthcare coverage to evaluate if cannabis use was detrimental to ART adherence.

Methods

Data for this study was obtained from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing observational prospective cohort of HIV-positive illicit drug users. The study participants were recruited using community-based methods including snowball sampling and extensive outreach in Vancouver's Downtown Eastside (DTES) and among local HIV/AIDS service organizations. Following recruitment and the provision of informed consent, participants complete an extensive interviewer-administered questionnaire, provide a blood sample, and complete a nurse-administered questionnaire and examination. Follow-up occurs semi-annually. ACCESS recruitment is ongoing and

includes the following criteria: individuals must be HIV-infected, aged 18 years or older, English speaking, and having used illicit drugs other than cannabinoids in the month prior to enrollment. ACCESS has been approved by the Providence HealthCare/University of British Columbia research ethics board.

Data from the semi-structured interviews is augmented with data on HIV care, ART medication exposure, and treatment/clinical outcomes obtained via a confidential linkage to the British Columbia Centre for Excellence in HIV/AIDS' Drug Treatment Program(BC-CfE), as described elsewhere (Wood et al., 2008). The BCCfE runs a centralized antiretroviral therapy dispensary for the province of British Columbia, and provides ART dispensing information on each participant in the ACCESS study. In addition to this, the program also contains an HIV/AIDS monitoring lab that provides full retrospective and prospective CD4+ cell count and plasma HIV-1 RNA viral load (pVL) observations for each participant in the study. Of note is the fact that all HIV care is provided free of charge to every PLWHA living in the province of BC, allowing us to analyze adherence to treatment free of the confounding influence of financial status.

Our main outcome, adherence to prescribed ART, was based on a pharmacy refill measure and was defined as the number of days ART was dispensed divided by the number of days the participant was eligible for ART in the previous six months. The outcome was further dichotomized into optimal adherence vs. sub-optimal adherence (≥95% vs. <95%). This validated measure using pharmacy refill data has been previously shown to be strongly associated with both virological suppression and survival (Palepu et al., 2001; Wood et al., 2003a; Wood et al., 2003c).

This study included all ACCESS participants who were exposed to ART at baseline and who had a CD4+ and viral load (pVL) observation within ±180 days of recruitment, and contributed at least one follow-up interview after the baseline interview. Individuals who initiated ART following recruitment were added and the date of the first interview following initiation was the baseline date. The primary explanatory variable of interest was high-intensity cannabis use, defined as at least daily self-reported cannabis use in the previous six-month period.

In order to estimate the relationship between high-intensity cannabis use and adherence to ART, we considered a number of secondary explanatory variables we hypothesized might confound this relationship including: age (per year older); gender (female vs. male); Aboriginal ancestry (yes vs. no); educational attainment (<high school diploma vs. >high school diploma) and formal employment in the previous six months (yes vs. no). The formal employment variable was defined, as in previous studies (Richardson, Wood, Li & Kerr, 2010), as having a regular job with a salary or temporary work in the six-month period prior to the interview. Individual-level and illicit drug use and related variables included; methadone maintenance therapy (yes vs. no); frequent cocaine injection (≥daily vs. <daily); frequent heroin injection (≥daily vs. <daily); frequent crack inhalation (≥daily vs.<daily) and daily binge alcohol use (>4 drinks per day-yes vs. no). We used the Center for Epidemiological studies Depression scale (CES-D) to measure depression. The variable was dichotomized (scores ≥16 vs. <16) with individuals who scored greater than 16 considered

regarded as being depressed. The CES-D has been shown to be a reliable and valid indicator of mild to severe depression with a reliability rating of Cronbach's Alpha (0.85) (Low-Beer & Chan, 2000; Radloff, 1977).

Clinical variables included: CD4+ cell count (per 100 cells/mL); plasma HIV-1 RNA level (copies/mL, per log10 increase); time elapsed since HIV diagnosis (measured in months); a protease inhibitor (PI) as part of the ART regime (yes vs. no) at the time of ART initiation and HIV experience of the prescribing physician (less than six patients vs. ≥ six patients). The HIV experience of the prescribing physician was defined, as in previous studies (Sangsari et al., 2012), as the number of patients that the participant's prescribing physician had previously enrolled in the province-wide HIV treatment registry at the time of ART initiation for the participant. Additional structural variables found to influence ART adherence in similar populations were also included in the analysis including homelessness and incarceration (Milloy et al., 2011, Palepu et al., 2011). Homelessness was defined as living on the street or having no fixed address in the past six months (yes vs. no), and incarceration was defined as being in a detention centre, jail, prison or penitentiary overnight or longer at least once in the past 6 months (yes vs. no).

As an initial step, we compared selected demographic (age, gender, Aboriginal ancestry, education, formal employment, downtown eastside residency), behavioural (at least daily drug use including-injection heroin, injection cocaine, crack cocaine; binge drug use; binge alcohol use) and clinical (methadone maintenance, physician experience, HIV-1 viral load, CD4+ cell count) characteristics among those who did and did not report at least daily cannabis use at baseline. We tested for group differences using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Next we performed bivariate and multivariate generalized linear mixed-effects models to examine the association between the variables of interest and their impact on adherence to ART. This type of regression modelling was used to account for the correlation between data gathered over time from the same participant and to best estimate the independent effect of high-intensity cannabis use on the likelihood of non-adherence in each participant. After examining bivariate associations we constructed a multivariate model, designed using an *a priori* modelling strategy (Maldonado & Greenland, 1993). We fitted a multivariate model, which included our primary explanatory variable, with the full set of secondary explanatory variables, noting the value of the coefficient associated with ART adherence. Next, we utilized a stepwise approach and constructed reduced models, each model with one of the secondary explanatory variables removed from the full set of explanatory models. Through comparison of the value of the coefficient for the primary variable in the full model and the reduced models, we identified the secondary variable that resulted in the smallest relative change to the coefficient. We then removed this variable and continued with the comparisons. The process was continued until the maximum change for the value of the coefficient for ART adherence from the full model exceeded five percent. This type of modelling strategy has been utilized previously to best estimate the independent relationship between an outcome of interest with several selected confounding variables (Maldonado & Greenland, 1993; Marshall et al., 2009; Milloy et al., 2011).

Results

Between May 2005 and April 2012, 523 individuals were recruited who were ART-exposed, had complete clinical information and were eligible for the study. In the analytic sample 188 (36%) participants were female and 194 (37.1%) participants reported Aboriginal ancestry.

The baseline characteristics of the sample stratified by at least daily cannabis use are presented in Table 1. At baseline at least daily cannabis smokers were: younger (44.2 years vs. 46.6 years, $p = 0.002$); more likely to be male (17.8% vs. 5.36%; $p < 0.001$); more likely to have completed high school (14.7% vs. 8.4%; $p = 0.04$); and more likely to drink less than four alcohol drinks daily (15.7% vs. 7.5%; $p = 0.004$).

Table 2 presents the bivariate associations between each explanatory variable and ART adherence over the study period. We did not observe a significant association between at least daily cannabis and ART adherence in a bivariate analysis (Odds Ratio [OR] = 0.91; 95% Confidence Interval [95% CI]: 0.63-1.30, $p = 0.359$). Female gender, homelessness, daily alcohol, daily heroin injection, daily cocaine injection, daily crack use, incarceration, and higher viral load were all negatively associated with optimal adherence in bivariate comparisons. Whereas older age, enrollment in MMT, ART regimes containing a PI, and higher CD4+ count were all positively associated with effective adherence to ART.

Results from the multivariate model results can also be found on Table 2. After adjustment for pVL, ART regimen and engagement in MMT, high intensity cannabis use (Adjusted Odds ratio [AOR] 1.12; 95% CI: 0.76-1.64, $p = 0.555$) was not significantly associated with ART adherence.

Discussion

In this long-term longitudinal study of ART-exposed PWID, we did not observe a significant association between greater than daily cannabis use and ART adherence. Specifically, we did not find any evidence indicating that daily or more frequent cannabis use compromises effective HIV treatment. It has been previously shown that HIV-infected PWID who are able to achieve adherence levels ≥95% are able to derive the clinical benefis of HIV-1 RNA viral suppression and CD4+ cell count increases (Wood et al., 2003a; Wood et al., 2003b; Wood et al., 2003c)

Our finding specific to cannabis use and adherence is in line with a number of studies conducted among PLWHA. A cross-sectional study that examined symptom management, cannabis use and its association with adherence among 178 PLWHA in Northern California did not find a statistically significant association between cannabis use and adherence, while adherence was negatively associated with other forms of illicit drug and alcohol use (De Jong et al., 2005). In addition, among participants who experienced moderate to severe nausea, cannabis users were more likely than non-cannabis users to report effective adherence to ART. In other observational studies among convenience samples of PLWHA in Canada and the U.S., PLWHA have reported cannabis to be an effective medication for the amelioration of symptoms associated with HIV and ART side effects, with some users suggesting its use improves their adherence to ART (Prentiss et al., 2004;, Ware, et al.,

2003). While we did not examine cannabis use for symptom management, these findings are similar to our results, where cannabis use did not significantly impact adherence. However, our results contradict those of a few studies that have found cannabis use to be associated with sub-optimal adherence to ART. A recent study that compared at least daily users, monthly users and non-users, found daily cannabis use to be associated with sub-optimal adherence and greater number of HIV-related symptoms (Bonn-Miller, Oser, Bucossi, & Traffton, 2012). The authors could not distinguish if sub-optimal adherence in the daily cannabis group was the result of a higher symptom burden or high intensity cannabis use and had inconsistent findings within their self-reported adherence measures. In a study of 775 PLWHA from Africa, Puerto Rico and the United States comparing cannabis use and over-the counter medications for symptom management amongst PLWHA, participants who reported cannabis use were more likely to self-report poor adherence (Corless et al., 2009). Another cross-sectional study of 200 PLWHA based in Australia, found that participants who reported cannabis use greater than 4 times per week had increased odds of poor adherence (Wilson, Doxanakis & Fairly, 2004). However, it should be noted that all of these studies were likely limited by their cross-sectional nature with a restricted number of possible confounding variables. In addition, in all of these studies adherence was measured by self-report, which has been found to be of limited validity (Kerr, Walsh, Lloyd-Smith & Wood, 2005; Kerr et al., 2008). To date, we are unaware of any other analysis that has examined high intensity cannabis use and adherence to ART longitudinally in a population of PWID who have free medication and healthcare access. We also utilized pharmacy refill data as a measure of adherence and consistent with our measure, optimal adherence was strongly associated with higher CD4+ cell counts and lower pVL.

Despite growing legal access to cannabis for PLWHA in Canada/North America and growing evidence of its effectiveness for symptom management in HIV care (Abrams et al., 2003; Abrams et al., 2007; Department of Justice Canada, 2011; Ellis et al., 2009; Haney et al., 2007) many healthcare practitioners remain reluctant to prescribe cannabis to patients (Belle-Isle & Hathaway, 2007). In order to support decisions to prescribe cannabis and cannabinoids, physicians will require additional evidence regarding the long-term impact of cannabis use on the health of cannabis users. Physicians may also have concerns about prescribing cannabis when its psychoactive effects, including transient confusion and short-term memory impairment, may impact the patient's ability to adhere to their medications. One study of PLWHA who use cannabis found among participants experiencing HIV symptoms there was an increase in memory impairment (Cristiani Pukay-Martin, & Bornstein, 2004). While our study did not analyze adherence and memory impairment, our findings suggest daily cannabis use may not compromise effective adherence. There also may be concerns amongst practitioners related to cannabis being utilized for recreational or non-intended purposes and the potential for psychological addiction with chronic use (Zvolensky et al., 2008). While concerns regarding inappropriate use and addiction have not been addressed here, our findings suggest at least daily cannabis use does not compromise adherence in a population who use illicit drugs. Given the high prevalence (23.1%) of at least daily cannabis use in our population, healthcare practitioners may also wish to engage PLWHA in discussions about addiction, harm reduction and cannabis use to ensure individuals are informed about potential negative impacts associated with the use of

cannabis. Additional referrals to medical cannabis dispensaries, where ingestible forms of cannabis, and harm reduction education are available for clients, may be beneficial for frequent cannabis users. In addition, randomized trials of cannabis and cannabinoids are needed to fully understand their role in HIV symptom management and disease processes.

Our study may have limitations. First, we utilized a cohort with a history of illicit drug use that is comprised of individuals who live in a setting where access to ART medications and HIV care is free. As such, our finding may be limited to these individuals and not generalizable to different populations in other geographic areas. Our pharmacy refill measure may overestimate adherence in the sample, as it indicates the number of ART medications administered without capturing the actual ingestion of these medications. However, this measure has previously been shown to be an accurate predictor of virological suppression (Wood et al., 2003c) and in this study, it was strongly associated with improved immunological and virologic status. While we attempted to control for a number of potentially confounding variables, adherence to ART is extremely complex and, common to all observational studies, we cannot exclude the possibility of unmeasured confounding variables. Finally, we did not examine the impact of less than daily cannabis use for medical purposes or symptom management in PLWHA and ART adherence, which has been previously shown to have a positive association with improved adherence (De Jong et. al., 2005). Further studies that examine cannabis use patterns and symptom management amongst PLWHA may help determine if there are additional associated benefits of cannabis use and ART adherence.

In summary, we found almost a quarter of our ART-exposed PWID were at least daily cannabis users at baseline, and in a longitudinal analysis using a validated measure, high-intensity cannabis use was not associated with adherence to ART. These findings suggest cannabis may be utilized by PLWHA for medicinal and recreational purposes without compromising effective adherence to ART.

Acknowledgments

We thank the study participants for their contributions to the research, as well as current and past researchers and staff. We would specifically like to thank Deborah Graham, Tricia Collingham, Carmen Rock, Brandon Marshall, Caitlin Johnston, Steve Kain, Benita Yip, Jennifer Matthews and Kristie Starr for their research and administrative assistance. The study is supported by the US National Institutes of Health (R01-DA021525). This work was supported in part by a Tier 1 Canada Research Chair in Inner-City Medicine awarded to Dr. Wood. Dr. Milloy is supported by the Michael Smith Foundation for Health Research and the Canadian Institutes of Health Research.

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Table 1

Baseline characteristics of 523 ART-exposed illicit drug users stratified by at least daily cannabis use in the last six months, ACCESS study (n = 523)

Characteristic	Less than daily cannabis use 402 (76.9)	At least daily cannabis use 121 (23.1)	*p*-value
Age			
Median	46.6 (40.1 – 50.2)	44.1 (37.8– 48.3)	0.002
Gender			
Male	241 (60.1)	93 (76.9)	
Female	160 (39.9)	28 (23.1)	< 0.001
Aboriginal ancestry			
No	252 (62.7)	77 (63.6)	
Yes	150 (37.3)	44 (36.4)	0.849
Education			
< HS diploma	214 (53.2)	77 (63.6)	
≥ HS diploma	188 (46.8)	44 (36.4)	0.043
Employment[1]			
No	339 (84.3)	104 (85.9)	
Yes	63 (15.7)	17 (14.1)	0.663
DTES resident[1]			
No	197 (49.0)	68 (56.2)	
Yes	205 (51.0)	53 (43.8)	0.165
MMT, current			
No	204 (50.8)	69 (57.1)	
Yes	198 (49.2)	52 (42.9)	0.225
Alcohol use[4]			
< 4 drinks/day	323 (80.3)	82 (67.8)	
≥ 4 drinks/day	79 (19.7)	39 (32.2)	0.003
Heroin injection[4]			
< Daily	345 (85.8)	103 (85.1)	
≥ Daily	57 (14.2)	18 (14.9)	0.847
Cocaine injection[1]			
< Daily	365 (90.8)	110 (90.9)	
≥ Daily	37 (9.2)	11 (9.1)	0.969
Crack cocaine use[1]			
< Daily	244 (60.7)	80 (66.1)	
≥ Daily	158 (39.3)	41 (33.9)	0.281
Binge drug use[1]			
No	315 (78.4)	101 (83.5)	
Yes	87 (21.6)	20 (16.5)	0.221

Characteristic	Less than daily cannabis use 402 (76.9)	At least daily cannabis use 121 (23.1)	*p*-value
Adherence[1]			
< 95%	177 (44.03)	59 (48.8)	
≥ 95%	225 (60.6)	62 (51.2)	0.359
CD4+ cell count			
Median (IQR)	2.9 (1.7 – 4.1)	2.9 (1.9 – 4.4)	0.569
Plasma HIV-1 RNA			
Median (IQR)	3.1 (1.6 – 4.4)	3.2 (1.6 – 4.4)	0.979
HIV MD experience			
Median (IQR)	52 (13 – 139)	51 (13 – 131)	0.859

[1] Refers to six month period prior to interview

Table 2

Longitudinal bivariate and multivariate mixed-effects analyses of factors associated with ≥95% adherence to ART in the previous six months, ACCESS study (n = 523)

Characteristic	OR[1]	95% CI[2]	p-value	AOR[3]	95% CI[2]	p-value
Cannabis use (≥daily vs. less)[4]	0.91	0.63 – 1.30	0.618	1.12	0.76 – 1.64	0.555
Age (per year older)	1.07	1.04 – 1.10	< 0.001	0.98	0.95 – 1.01	0.351
Gender (Female vs. male)	0.57	0.37 – 0.88	0.010	0.76	0.51 – 1.13	0.186
Aboriginal ancestry (Yes vs. no)	0.50	0.32 – 0.76	0.70	0.70	0.47 – 1.03	
Homeless (Yes vs. no)	0.44	0.28 – 0.71	< 0.001			
Education (≥HS diploma vs. less	1.14	0.75 – 1.74	0.515			
Alcohol (≥4 drinks vs. less)[4]	0.69	0.50 – 0.94	0.021	0.82	0.58 – 1.16	0.276
CM injection (≥daily vs. less)[4]	0.58	0.20 – 1.67	0.316			
Heroin injection(≥daily vs. less) [4]	0.33	0.21 – 0.49	< 0.001			
Cocaine inject (≥daily vs. less)[4]	0.62	0.40 – 0.95	0.027			
Crack use (≥daily vs. less)[4]	0.49	0.37 – 0.65	< 0.001			
Incarceration (Yes vs. no)[4]	0.54	0.36 – 0.82	0.004			
MMT (Yes vs. no)	2.65	1.91 – 3.68	< 0.001	1.49	1.08 – 2.06	0.015
CESD score (≥16 vs. <16)	0.98	0.70 – 1.35	0.902			
Employment (Yes vs. no)[4]	1.25	0.86 – 1.73	0.254			
Time since HIV (per month	1.00	0.99 – 1.00	0.954			
Regimen includes PI (Yes vs. no)	11.71	8.30 – 16.50	< 0.001	6.41	4.62 – 8.88	< 0.001
CD4+ cells (Per 100 cells/mm^3)	1.51	1.37 – 1.65	< 0.001			
Plasma HIV RNA/mm^3 (log10)	0.34	0.30 – 0.38	< 0.001	0.36	0.37 – 0.41	< 0.001
HIV MD (≥ 6 patients vs. less)	1.60	0.98 – 2.86	0.057			

[1] Odds Ratio

[2] 95% Confidence Interval

[3] Adjusted Odds Ratio

[4] Refers to the six month period prior to the interview