ANTIRETROVIRAL ADHERENCE AND PRESCRIBED CANNABIS USE IN A POPULATION OF PEOPLE LIVING WITH HIV/AIDS

by

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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 possible 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. In order to identify which PLWHA are accessing prescription cannabis, we also examined prevalence and correlates of those receiving a prescription for cannabis in the past six months.

**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. Using a cross-sectional design and bivariate statistical methods we also examined the prevalence and correlates of prescribed cannabis.

**Results:** From May 2005 to May 2012, 523 HIV-positive illicit drug users were recruited and contributed 1215 person-years of observation. 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 ART (Adjusted Odds Ratio = 1.12, 95% Confidence Interval [95% CI]: 0.76 – 1.64, p-value = 0.555). From November 2011 to December 2012, 519 HIV-positive illicit drug users were surveyed, and in cross-
sectional analysis, 81 (15.6%) individuals reported receiving a prescription for cannabis in the past 6 months. We found no significant differences among those who were and were not prescribed cannabis.

**Conclusions:** High-intensity cannabis use was not associated with adherence to ART. A number of PLWHA report receiving a prescription for cannabis use. These findings suggest cannabis continues to be utilized by PLWHA for medicinal and recreational purposes without compromising effective adherence to ART.
Preface

I am extremely grateful for the opportunity and support provided from the entire team at the Urban Health Research Initiative as I worked with data from the ACCESS study. As the primary author I performed the literature review, selected the variables to include in the modeling, defined the type of analysis utilized and interpreted the results. The support of my supervisor Dr. Lynda Balneaves, the ACCESS study Co-Principal Investigator Dr. M-J Milloy and committee member Dr. Thomas Kerr were integral to the iterative process of the construction and explanation of the modeling procedures utilized in the multi-variate analysis, including the selection of confounding variables and also invaluable in providing comments on earlier draft of this thesis. Thesis supervisor Dr. Lynda Balneaves, committee members Dr. Thomas Kerr and Dr. Joy Johnson also provided additional editing and proofreading support during the completion of thesis. It should also be mentioned, additional statistical support was received from Annick Simo, who ran the longitudinal bivariate and multivariate analysis and provided statistical results for the thesis. The candidate, however, performed the interpretation and analysis of the findings.

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This research study “The effects of cannabis use on adherence to HARRT among HIV-positive injection drug users” was reviewed and approved by the UBC-Providence Health Care Research Ethics Board. UBC-PHC REB Number: H05-50233.
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List of Abbreviations

ACCESS- Aids Care Cohort for the Evaluation of Support Services

ART- antiretroviral therapy

CTP- cannabis use for therapeutic purposes

CMA- Canadian Medical Association

CNS- central nervous system

CI- confidence interval

DTP- drug treatment program

HAART- highly active antiretroviral therapy

HAND- HIV associated neurocognitive disorders

HIV- human immunodeficiency virus

MMAP- Medical Marijuana Access program

MMAR- Medical Marijuana Access Regulations

NRTI- nucleoside reverse transcriptase inhibitors

NNRTI- non- nucleoside reverse transcriptase inhibitors

OR- odds ratio

PI- protease inhibitors

PLWHA- people living with HIV/AIDS

pVL- plasma HIV-1 RNA viral load

PWID- people who use illicit drugs

THC- Tetrahydracannabinol
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Chapter 1: Introduction

Cannabis has been utilized for medicinal purposes for several centuries (Kalant, 2001). In 2001 the Government of Canada amended the Controlled Drug and Substances Act and created Marihuana Medical Access Regulations (MMAR), which allowed patients to legally utilize cannabis to manage the symptoms associated variety of illnesses including HIV/AIDS (Government of Canada, 2011). Symptoms of HIV/AIDS covered in the MMAR include: anorexia, poor appetite, pain, neuropathic pain, nausea/vomiting (Health Canada, 2011). In descriptive studies, people living with HIV/AIDS (PLWHA) have reported cannabis use as an effective medication for managing a number of HIV related symptoms including appetite stimulation, anorexia, stress, nausea/vomiting, and pain (Belle-Isle & Hathaway, 2007; Prentiss, Power, Balmas, Tzuang & Israelski, 2004; Ware, Rueda, Singer & Kilby, 2003). In addition to managing symptoms associated with HIV disease processes, PLWHA have also reported using cannabis to manage the side effects of antiretroviral therapy (ART) medications including: gastro-intestinal upset, insomnia, and peripheral neuropathy (Ware, et al., 2003). Effective symptom management can play a large role in improving the quality of life for patients suffering with HIV.

With improvements to ART medications and effective medication adherence, PLWHA are living longer and HIV is now considered a chronic illness. Because of the longer life expectancy and chronic nature of the disease, many PLWHA are exposed to ARV medications and HIV over a long period of time, resulting in a potential increase in adverse effects of ART. As a result, practitioners working with PLWHA must consider prescribing medications and therapies that promote effective symptom management and subsequently improve the quality of life for PLWHA.
To date very little research has described the prevalence and correlates of cannabis use for medical management of HIV and ART-related symptoms. In addition, very little data exists that describes the clinical characteristics and medication regimens of PLWHA who report using cannabis for medical purposes. No long-term prospective studies assessing the demographic, clinical and structural correlates of prescribed cannabis use have been conducted within a setting of universal healthcare, where PLWHA also have legal access to cannabis for therapeutic use. As professionals whose primary goal is to help and support people living with HIV manage their illness and improve the quality of their lives, healthcare providers require more evidence about the characteristics and experiences of HIV-positive individuals who report HIV symptom management with prescribed cannabis. This information will help support decision making, policy development and prescribing practices that involve using cannabis as a potential intervention for effective symptom management of HIV.

Since the introduction of highly active ART (HAART), PLWHA have experienced significant gains in HIV-related morbidity and mortality (Hogg et al. 1998; Lima et al., 2007). HAART involves combining several antiretroviral medications that target different areas of HIV reproduction, in order to diminish the virus’s ability to replicate. While a small number of PLWHA remain on single or dual ART options, ART regimes usually include a combination of two nucleoside reverse transcriptase inhibitors (NRTI) with either a non-nucleoside reverse transcription inhibitors (NNRTI) or a protease inhibitors (PI)(British Columbia Center for Excellence in HIV/AIDS, 2009). By combining these medications, clinicians are able decrease the amount of circulating virus in fluids like blood plasma, which diminishes the impact of the virus on immune cells and over time allows the body’s immune system CD4 cells to replenish (Montaner et al., 1998). ART also reduces HIV viral load, or the amount of virus in PLWHA’s
blood and circulating fluids, to undetectable levels. This reduction in viral load has benefit to HIV-positive individuals by promoting immune health, and also has the potential secondary public health benefit of reducing the rates of transmission of HIV in the general population (Wood et al., 2012). Recent research has indicated that by effectively adhering to ART medications individuals may protect their non-HIV sexual partners from acquiring the disease (Cohen, et al., 2011). HIV researchers speculate that, through the expansion of access to ART globally, the HIV epidemic could be effectively curtailed (Lima et al., 2008a). With improved ART regimes delivering potential benefits to both individuals and communities, the focus is increasingly turning to supporting adherence to ART in PLWHA and managing side effects associated ART.

The PLWHA who are able to maintain optimal adherence to HIV medications have improved life expectancy and reduced morbidity (Zwhalen et al., 2009). Optimal adherence is defined as greater than or equal to 95% adherent to ART therapy (Low-Beer, Yip, O’Shaughnessy, Hogg & Montaner, 2000a). Optimal adherence to ART adherence has been shown to be strongly associated with virological suppression of plasma HIV RNA (pVL), restoration of immunologic function and lengthened survival for PLWHA (Hogg et al. 1998; Low-Beer et al., 2000a; Pallela et al. 1998 ). Unfortunately for PLWHA, in order to be effective, ART requires sustained adherence and patients are expected to be on these medications for life (Lima, et al., 2008b). If optimal adherence is not achieved, HIV virus mutations and drug resistance may occur, limiting ART treatment options and subsequently increasing an individual’s risk of hospitalization and death (Fielden et al., 2008; Hogg, et al., 2006). Sub-optimal adherence and subsequent increase in viral load may also increase the risk of HIV transmission and the transmission of drug resistant strains of HIV in the greater community.
(Hogg et al., 2006; Wood et al., 2008). As a result, there has been great interest within clinical and research communities regarding strategies, that may enhance adherence to ART.

Adherence to HAART can present a number of challenges for individuals. Although dosing regimens have improved in recent years, many regimens can be complex and require multiple doses at various points during the day. Often, effective absorption of ART medications requires that medications are taken with food or with dietary restrictions, which may present difficulty for individuals with food security issues and individuals who lack appetite (Ferguson, Stewart, Funkhouser, Tolson, Westfall & Saag, 2002). Many medications in ART regimes are associated with side effects that need to be managed, to help encourage effective adherence. If these side effects are not effectively managed, they can undermine individual adherence behaviour and can result in the discontinuation of HAART. Lastly, the cost of paying for medications can be prohibitive for individuals of lower socio-economic backgrounds that live in countries where ART are not provided free of charge (McDonnell et al., 2006). In addition to the barriers to optimal adherence faced by PLWHA, there are additional personal, social and structural factors that can influence effective adherence amongst PLWHA who use illicit drugs (PWID) (Malta, Magnanini, Strathdee & Bastos, 2010).

PWID account for a substantial number of existent and newly diagnosed cases of HIV in Canada. PWID often become infected with HIV by sharing contaminated drug equipment and represented 17% of new HIV diagnoses in Canada in 2008 (Public Health Agency of Canada, 2011). Despite the advances in HIV treatment, PWID have frequently been found to exhibit sub-optimal adherence to ART and HIV/AIDS-related morbidity and mortality remains high in this population (Zwahlen et al., 2009; Wood et al. 2003). Amongst PLWHA, sub-optimal adherence has been associated with 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). Additional demographic characteristics and individual-level barriers to adherence have been identified amongst PWID populations and include: age; female gender; aboriginal ethnicity, alcohol use; lower self-efficacy; and psychiatric co-morbidities (Arnsten et al., 2007; Bouhnik et al., 2005; Carrièri et al., 2003; Hadland et al., 2012; Kerr et al., 2005a; Miller et al., 2006; Palepu et al., 2004a; Tapp et al., 2011). Recently social and structural barriers to effective adherence have also been identified such as homelessness and incarceration (Bouhnik et al., 2002; Milloy et al., 2011; Milloy et al., 2012; Palepu et al., 2004b; Palepu et al., 2011). Despite the risk active psychoactive drug use can present for non-adherence to ART, few studies have evaluated the relationship between cannabis use and 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). Cannabis use for therapeutic purpose (CTP) has been reported by PLWHA to help manage a number of HIV-related symptoms including; appetite stimulation, 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., 2007a; Ellis et al., 2009; Haney et al., 2007), the evidence regarding cannabis use and the impact on adherence remains limited and, no long-term prospective studies assessing cannabis use as a factor that may affect adherence have been conducted within a setting of universal healthcare with publically-funded HIV care. The present study was conducted to investigate the role cannabis use among a cohort of PWID living with HIV/AIDS, to evaluate if cannabis use is detrimental to ART adherence.
1.1 Literature Review

1.1.1 Cannabis Use as Medication

There are a number of psychoactive compounds commonly referred to as cannabnoids found in the cannabis plant. Tetrahydracannabinol (THC) is the cannabinoid that typically accounts for most of the physical and psychological effects seen in patients and cannabis users. THC acts on two types of cannabinoid receptors CB1 and CB2. The CB1 receptors are found mainly in the brain and CNS and account for many of the psychoactive and physiological responses to cannabis (Galièegue, et al., 1995; Grotenhermen, 2003). Cannabinoids have been identified as potent anti-inflammatories in studies examining their effect on in vitro and in vivo animal samples (Klein et al., 2003) CB2 receptors are located primarily in the immune cells and neurons, which may account for the anti-inflammatory action of THC. In addition to the pharmacodynamics research on cannabis, there is a growing body of scientific data that suggests cannabis can be used for acute management of a variety of symptoms including nausea, vomiting, anorexia (i.e., wasting syndrome), pain, neuropathic pain, muscle spasticity and depression and anxiety (Grotenhermen, 2003; Kalant, 2001). Cannabis has been utilized by individuals to ameliorate symptoms related to a number of diseases including HIV/AIDS, cancer, multiple sclerosis, anorexia, rheumatoid arthritis, arthritis, glaucoma, asthma, and mood disorders (Clark et al., 2004; Grotenhermen, 2003; Ware, Adams, & Guy, 2005).

Cannabinoid use for HIV related symptoms and AIDS-related conditions has been examined in a number of observational studies. Early studies highlighted cannabis use as an effective complementary medicine to encourage appetite stimulation, which helped prevent the muscle wasting and anorexia associated with HIV (Beal et al., 1995; Beal et al., 1997). Cannabis use in the treatment of nausea and vomiting related to HIV illness and medications has also been
examined in observational studies (de Jong, Prentiss, McFarland, Machekano & Israelski, 2005; Lane et al., 1991). In addition to the descriptive evidence on the use of cannabis in PLWHA populations, randomized control trials have been performed to assess the effectiveness of cannabis in the treatment of symptoms associated with HIV/AIDS. These studies have focused on the use of smoked cannabis to treat HIV-sensory neuropathic pain a condition that impacts an estimated 30% of PLWHA and is the most common symptom of HIV disease (Ellis et al., 2009). In a double-blinded, crossover trial, Ellis et al. (2009) found that smoked cannabis as an adjunct to “concomitant analgesic use” was effective in treating neuropathic pain as compared to a placebo. The authors found that cannabis use improved neuropathic pain management with minimal side effects. Improvements to mood and daily functioning were also reported by the study participants. Another double-blinded randomized clinical trial (RCT) of the effectiveness of smoked cannabis in the treatment of neuropathic pain found that 34% of the smoked cannabis group reported a decrease in daily pain as compared to 17% in the placebo group ($p=0.03$) (Abrams et al., 2007a). The authors also found pain reduction greater than 30% was reported in 52% of the smoked cannabis group as compared to 24% in the placebo group ($p=0.04$). A common criticism of these studies that involve smoked cannabis and the use of a placebo relates to how difficult it is to blind study participants when a smoked substance like cannabis is used. As such, there is a potential for reporting bias if participants have had any previous exposure to cannabis.

1.1.2 Safety of Cannabis

There continues to be some debate about the safety and efficacy of prescribing medicinal cannabis within the scientific community (CMA, 2013). Short term adverse effects of cannabis use include: CNS depression, sedation, temporal and spatial distortion, impaired motor function,
impaired hand-eye coordination, short term memory impairment, mental confusion, anxiety and disorientation (Kalant, 2004). In addition, while the evidence is unclear related to the impact of long term cannabis use on the respiratory system, high-intensity or daily cannabis smoking has been associated with respiratory dysfunction in cannabis smokers (Hall & Degenhardt, 2009). Prescribing physicians may have concerns about safely prescribing cannabis when side effects like mental confusion and memory impairment may impact the patient’s ability to safely adhere to their medications. HIV-associated neurocognitive disorders (HAND), created when the HIV virus enters the CNS and damages nerves cells, is frequently found in PLWHA with more advanced HIV disease and can impact memory loss. One study examining memory impairment among PLWHA who use cannabis, compared subjects with symptoms associated with more advanced HIV, with those who did not display symptoms (Cristiani, Pukay-Martin & Bornstein, 2004). The authors found participants experiencing HIV symptoms experienced an increase in memory impairment compared to participants who did not report experiencing HIV symptoms. The study relied on small samples sizes and failed to control for the confounding effect of HAND within the study participants. There are also concerns related to cannabis being utilized for recreational or non-intended purposes and the potential for psychological addiction with chronic use (Bonn-Miller, Oser, Bucossi, & Traffton, 2012; Zvolensky et al., 2011). In addition to the acute side effects, chronic effects might also include bronchitis, emphysema, tachycardia, postural hypotension and decreased sperm counts (Crowford, 2003).

A recent systematic review of safety studies of medicinal cannabis over the past 40 years examined 23 RCTs and 8 observational studies and concluded that with short term use the rates of non-serious adverse events were higher among medical cannabis users then controls (rate ratio = 1.86, 95% Confidence Interval (95% CI): 1.52-2.21) and the rates of serious adverse events did
not differ between groups (rate ratio= 1.04, 95% CI: 0.78-1.39) (Wang, Collet, Shapiro & Ware, 2008). The authors also identified that risks associated with long term use were poorly characterized and further research is required to help guide health policy and medical professionals.

There are concerns that cannabis use may diminish the immune response in PLWHA. Cannabinoids (CB2) potent anti-inflammatory action may impair immune response by impacting inflammatory mechanisms, which help mediate immune response to viruses (Klein et al., 2003). Previous in vitro and in vivo studies examining the influence of cannabinoids on the immune system to viruses, have found that cannabinoids diminish the immune response to HIV (Reiss, 2010). The research on smoked cannabis and cannabinoids in human subjects is limited, however one observational study of medical and recreational use of cannabis amongst PLWHA, so found no significant differences in CD4+ cell counts amongst cannabis users (Furler et al., 2004).

A few studies have examined the impact of cannabis use on ART drug levels and particularly PI medications. A study examining drug levels of atazanavir amongst 32 PLWHA cannabis users, found the median atazanavir trough concentrations were lower amongst cannabis users in comparison to non-users and that 50% of cannabis users had trough concentrations below the therapeutic range (Ma et al., 2009). The lower drug levels, however, did not have an impact on the clinical markers viral load or CD4 count in the sample. An additional RCT of the effects of smoked cannabis and dronabinol use on PLWHA receiving the PI’s indinavir and nelfinavir found the maximum blood plasma concentration of these drugs to be slightly lower amongst cannabis smokers (Kosel et al., 2002). However the author’s did not find concurrent dronabinol and cannabis use to have any clinically significant short-term effects or adverse impacts on plasma viral load and CD4 counts. In a short-term RCT of patients on the PI’s
indinavir and nelfinavir, where the authors examined the impact of cannabinoids on immune response, the results indicated there were no statistically significant decreases in CD4 and CD8 cell levels or plasma drug levels in patients using smoked cannabis or drabinol as compared to a placebo group (Abrams et al., 2003). Both groups using smoked cannabis or oral cannabanoid medications, showed an increase in CD4 and CD8 cell counts as compared to the placebo group.

1.1.3 Prevalence of Cannabis Use in PLWHA

To date a number of observational studies have focused on the prevalence of cannabis use for symptom management in HIV populations. In a cross sectional study based on survey data from participants enrolled in the British Columbia Center for Excellence Drug Treatment Program (DTP) between October 1998 and September 1999, 14% of respondents reported using cannabis for medicinal purposes (Braitstein et al., 2001). The DTP dispenses medications for the majority of PLWHA in the province of British Columbia, so the sample reflects a good representation of PLWHA living in the province and on medications. A multivariate analysis of factors associated with cannabis use found that experiencing gastrointestinal side effects and peripheral neuropathy were positively and independently associated with cannabis use. Medicinal cannabis users were more likely to be male and younger in age. The data is based on figures from 1998-1999, shortly before the MMAR was introduced and may be out of date with current prevalence patterns. The authors also conclude that PLWHA are using cannabis to manage gastrointestinal side effects and peripheral neuropathy. These HIV-related side effects are frequently reported by PLWHA (Nicholas et al., 2007; Obrien, Clark, Besch, Lynn-Myers & Patricia, 2003). The study did not examine the recreational use of cannabis, cannabis use and adherence or the clinical characteristics of those who report using (CTP).
An additional cross-sectional study based in eastern Canada surveyed 160 participants recruited from HIV clinics in Toronto, Montreal and Ottawa and 19 participants from one compassion club about their use of cannabis and the synthetic cannabinoid dronabinol which is available in pill form. In the sample 59 participants (37%) reported current use of cannabis. One hundred and fourteen (70%) participants reported experiencing adverse effects related to ART, with 23 participants (14%) indicating these adverse effects negatively impacted their level of adherence. Just over a quarter of participants (28%) reported the use of cannabis or dronabinol to manage the side effects of ART. In addition to these findings, 7% of participants reported the use of cannabis or dronabinol improved their adherence to ART. Up to 37% of the participants also reported cannabis use for HIV symptom management (Ware et al., 2003). Participants reported using cannabis to effectively manage symptoms including stress relief, loss of appetite, weight loss, pain, and nausea and vomiting. Although study design limitations prevented causal relationships between cannabis use and improved adherence to HAART from being inferred, the potential supportive role of cannabis in symptom management and medication adherence in PLWHA is intriguing. The possible benefit, however, must be balanced against the side effects reported by study participants including euphoria (87%), dry mouth (63%), drowsiness (45%), paranoia and heart palpitations (26%) and anxiety (25%).

A cross-sectional survey and retrospective chart review conducted in Ontario, Canada between 1999 and 2001 examined the prevalence and predictors of medicinal cannabis use amongst a convenience sample of 104 PLWHA (Furler, Einarson, Millson, Walmsley & Bendayan, 2004). In the sample, 43% of participants reported any cannabis use and 29% reported CTP. Of the CTP users the most common reasons provided for use included: appetite stimulation (70%); sleep/relaxation (37%); nausea/vomiting (33%); pain management (20%) and
anxiety/depression (20%). The recreational cannabis users were more likely to be male and have a history of intravenous drug use. In a multivariate analysis, only having a mean income less than $20,000 was found to be predictive of medicinal cannabis use. The authors also did not examine negative side effects of cannabis use.

Another cross-sectional study conducted in Northern California, United States (US), documented the prevalence of cannabis use for symptom management amongst a convenience sample of 252 PLWHA recruited from 3 public health clinics, and found that 23% of participants reported using cannabis in the past month. Of those who reported recent cannabis use, 44% participants reported using cannabis to manage symptoms including nausea, anorexia, pain, anxiety and depression (Prentiss et al., 2004). Bivariate analysis identified participants experiencing moderate to severe nausea as being more likely to have used cannabis (Odds Ratio [OR] = 3.1, 95% CI: 1.6–5.9). The researchers did not examine whether the source of nausea was related to ART medications or symptoms of HIV disease. The authors also did not examine negative side effects of cannabis use.

An additional study based in California, US examined a convenience sample of 1746 CTP users, and reported on therapeutic benefits of cannabis (Reinarman, Nunberg, Lanthier & Heddleston, 2011). The most common benefits reported were: pain relief (83%); improved sleep (71%); reduced muscle spasms (41%) and headaches (41%); anxiety relief (38%); improved appetite (38%); and decreased nausea and vomiting (28%). Another interesting reported benefit, related to the lack of universal medical coverage in the US, was the use of CTP as a substitute for prescription medication, by 51% of the participants. The author’s suggested that participants might be utilizing CTP because they lacked sufficient medical insurance to cover the cost of prescribed medications. The authors also discussed the potential for recreational users to
fabricate medical conditions or symptoms in order to obtain legally sanctioned access to cannabis. This would allow recreational consumers a way to avoid legal penalty. The authors suggested it is difficult to assess the magnitude of this phenomenon, but it is plausible given the harsh legal penalties associated with illegal use in the US.

A cross-sectional study based in the United Kingdom (UK), where cannabis is not legal for medicinal purposes, found a significant number of PLWHA were using CTP. The sample consisted of 143 participants who attended a large outpatient clinic for HIV care and reported CTP to treat symptoms associated with HIV (Woolridge et al., 2005). Study participants reported the following symptoms were effectively treated via CTP: improved appetite, muscle pain, nausea, anxiety, nerve pain, and depression. The authors did not assess for negative side effects of cannabis use, but found 47% of respondents reported “memory deterioration” due to cannabis use (Woolridge et al., 2005, p.361). The authors concluded that patient use of cannabis for symptom management is highly prevalent despite significant legal barriers in the U.K.

### 1.1.4 Symptom Management and Adherence to ART

Given the importance of adherence to HAART medication in increasing the effectiveness of treatment and decreasing morbidity and mortality in PLWHA, identifying medications like cannabis that can ameliorate the side effects of HAART may help reduce the number of PLWHA who fail to achieve optimal adherence. As described earlier, side effects of ART medications, particularly nausea and vomiting, are frequently reported as a reason for poor adherence rates and even discontinuation of medication regimes altogether (O’Brien et al., 2003; Prentiss et al., 2004). To date, the evidence on cannabis use and adherence to ART is limited and contradictory. In the two Canadian studies previously discussed, researchers identified that PLWHA may be using cannabis to manage symptoms of ART medications. In Ware and colleagues’ study (2003)
a small portion of PLWHA (7%) reported cannabis use helped to improve their medication adherence. A recent cross sectional study based in San Francisco, California compared cannabis use intensity, incidence of HIV symptoms and side effects to ART and adherence to ART medications (Bonn-Miller, Oser, Bucossi, & Trafiton, 2012). The authors compared three groups, participants who used cannabis daily, less than daily and those who did not use cannabis. They found participants who reported daily or greater cannabis use had worse symptoms and poorer adherence than those who used cannabis weekly and those who did not use cannabis. The authors concluded it was unclear whether the intensity of cannabis use or the greater number of reported side effects and symptoms were the cause of ineffective adherence in the daily cannabis user group. The study was limited by its cross-sectional design and inconsistencies in ART adherence measurements between groups. The study also failed to include a number of potential confounders that have been found in previous studies of ART adherence to have a significant impact on effective adherence.

A cross-sectional study of 178 PLWHA in Northern California found that 24% of the participants reported using cannabis in the previous month (de Jong et al., 2005). The authors did not find a statistically significant association between cannabis use and adherence (OR = 0.90, 95% CI: 0.4–1.9, p = 0.83), however adherence was negatively associated with illicit drug use and alcohol use. The authors further stratified cannabis use based on symptoms including moderate to severe nausea. Among those who reported moderate to severe nausea, cannabis users were more likely than non-cannabis users to report effective adherence to ART (OR 3.30, p= 0.07). The authors also found participants without nausea who used cannabis, reported lower rates of adherence when compared to non-cannabis users. The sample sizes for the regression analysis in this study were quite small possibly limiting the inclusion of factors associated with
adherence, including housing and incarceration. In addition the authors relied on a weak measurement of adherence, specifically self-reported adherence over the past week, with those who missed one dose considered non-adherent. This type of measurement has the potential to overestimate non-adherence and adherence rates (Kerr, Walsh, Lloyd-Smith & Wood, 2005). The authors also failed to stratify illicit drug use by specific drugs, which may have confounded the study findings.

1.1.5 Cannabis, Drug Use and Adherence to ART

There is some concern within the HIV medical community that cannabis use may impede effective adherence to ART, by creating memory deficit and CNS disturbance. To date the evidence analysing the impact of cannabis use on adherence is limited and contradictory. In a cross-sectional study of adherence and sexual behaviour involving 255 PLWHA in the South Eastern U.S., participants who reported cannabis use in the past week reported poor adherence to ART (Kalichman & Rompa, 2003). The study did not include many personal and structural factors, which may have confounded the association between cannabis use and adherence. In addition, the authors did not find statistically significant differences in HIV clinical markers CD4+ count and viral load between adherent and non-adherent groups, suggesting the ‘self-report’ adherence measurement used may not have resulted in accurate measurements.

Another cross-sectional study of 2484 individuals based in France focused on drug use and adherence to HAART in a general population of PLWHA (Perreti-Watel, Spire, Lert & Obadia, 2006). The authors utilized data clustering to analyze multiple drug use patterns and found that cannabis use was associated with poor adherence when embedded with other drug use including heroin and alcohol use. The study relied on a poor measurement of adherence (i.e.,
based on self-report data) and also failed to measure clinical factors such as CD4+ and viral load, which help support adherence data conclusions.

An additional cross-sectional study involving 1910 participants receiving HIV-related care in US hospitals focused on non-adherence, mental health correlates and drug use (Tucker et al. 2003). In a multivariate analysis of drug use variables and adherence the authors found cannabis use to be associated with non-adherence (OR 1.71, 95% CI: 1.22-2.31). In an additional analysis in which they examined any drug use, alcohol use, mental health variables and adherence to ART, the authors did not find illicit drug use to be statistically significant with poor adherence. A further study of 764 PWID in Baltimore, US, found no association between cannabis use and non-adherence (Lucas et al., 2001). Currently no studies have examined cannabis use and adherence in exclusively PWID populations in settings like Canada where access to ART is free and medically prescribed cannabis exists. In addition to this, the existing research has relied on cross-sectional observation, poor definitions and measures of adherence and have not controlled for other potential confounding variables, including various structural factors, which may be impacting ART adherence.

1.1.6 Barriers and Facilitators to Adherence amongst PLWHA Who Use Illicit Drugs

A number of studies have identified barriers to optimal ART adherence in PWID populations. Active use of heroin, crack, and cocaine has been frequently but not consistently associated with poor adherence to ART among PWID participants (Crisp et al., 2004; Lucas et al.; 2001; Palepu et al., 2003; Peretti-Watel et al., 2006; Tucker et al., 2003). In addition to active drug use, alcohol use and depression in PWID subjects have been identified as factors associated with poor adherence (Bouhnik et al., 2005; Lima et al., 2007; Palepu et al., 2003). Many of these studies did not include cannabis as a potential predictor variable in their analyses.
Furthermore, many of the studies have taken place in environments where access to ART and HIV care can be negatively impacted by the cost of medications and healthcare, unlike the setting of this study. Further research is required to determine if an association between effective ART adherence and cannabis exists in PWID populations.

A further limitation of studies that have examined ART adherence amongst PWID was the failure to include structural factors that may confound the association between drug use and adherence to ART. Structural factors including; homelessness, incarceration and limited access to primary care and HIV services, have been identified as barriers that influence adherence and HIV care amongst PLWHA populations and are frequently experienced by PWID. Recent studies in PWID populations have included structural factors that may influence adherence to ART. Homelessness has been identified as a structural factor that negatively influences ART adherence (Knowlton et al., 2006; Milloy, et al, 2012; Palepu et al., 2011) Recent incarceration was also identified as a factor that can negatively impact HAART adherence and clinical outcomes for HIV-positive PWID in studies in Canada and the U.S. (Milloy, et al. 2011; Palepu et al., 2003; Small, et al., 2009; Waldrop-Valverde & Valverde, 2005). In addition to this, PWID who were able to access drug treatment through methadone maintenance therapy (MMT) achieved higher rates of adherence (Malta et al., 2008; Palepu et al., 2006). These findings highlight how drug using populations can benefit greatly from comprehensive medical services that include addiction support programs, social support and housing support services and address the complexity of clients suffering from addiction and other comorbidities like HIV. While these studies have examined active drug use and structural factors that may influence adherence, they have not included cannabis as a potential variable of interest in their analyses.
In summary, current research on cannabis use in PLWHA has focused primarily on cannabis’ role in symptom management. The majority of these studies have assessed self-reported cannabis use, in cross-sectional analyses and found PLWHA to report cannabis to be an effective medication for treatment of HIV-illness related symptoms. A few studies have examined the impact of cannabis use on adherence to ART, with some researchers reporting improved adherence and others identifying cannabis use associated with sub-optimal adherence. These studies have been limited by cross-sectional analyses, a limited number of confounding variables, poor measures of adherence, and a lack of clinical measures to support the validity of their findings (i.e., viral load). While practitioners are interested in identifying medications that support symptom management in PLWHA, the safety of prescribing cannabis and the impact on adherence is not well established. To date, no studies have examined the association between cannabis use and effective adherence to HARRT in a longitudinal cohort of PLWHA PWID.

1.1.7 Obtaining a Prescription for Cannabis: The Canadian Context

In 2001 the Government of Canada created the Medical Marijuana Access Regulations that permitted seriously ill individuals, including PLWHA to access cannabis for medical purposes. The MMAR permits the use CTP by PLWHA for the following HIV-related symptoms: pain, nausea/vomiting, appetite and anorexia (Government of Canada, 2011). Surveys of PLWHA based in Canada have found reported medicinal cannabis use to range between 17 to 37% amongst PLWHA populations (Brainstein et al., 2001; Furler et al., 2005; Ware et al., 2003). Since its inception, the MMAR and its administrative arm the Medical Marijuana Access program (MMAP) have been criticized by physicians and CTP users. CTP users have been critical of the MMAP’s inability to provide a safe and good quality cannabis product and suggest the application process was inefficient and created a barrier for many CTP applicants (Lucas et
al., 2012). In surveys of PLWHA reporting CTP, a limited number have obtained a prescription for legal cannabis use and a majority continue to rely on illegal sources to obtain cannabis (Belle-Isle & Hathaway, 2007).

In June 2013, the Government of Canada outlined a number of proposed changes to the MMAR including: the removal of the government’s role in the production and distribution of cannabis; the removal of the government’s role in providing authorization to individuals with healthcare practitioners would becoming the sole decision makers regarding eligibility for CTP; promoting the production of dried cannabis by licensed producers; and promoting the sale and distribution by specific regulated parties (Government of Canada, 2013). While a number of doctors have been supportive of PLWHA seeking legally sanctioned access to medicinal cannabis, a small number of PLWHA still face difficulties in obtaining support from their physicians and report having to visit a number of physicians before being granted access to CTP (Belle-Isle & Hathaway, 2007). Physician organizations have been critical of the MMAR and the proposed changes, suggesting until there is sufficient scientific evidence outlining the benefits, efficacy and potential long-term adverse effects of CTP it is improper for physicians to be the primary “gatekeepers” of CTP access (CMA, 2013). CTP user groups have also been critical of the proposed changes, suggesting they will increase cannabis costs for CTP users and limit availability to dried cannabis, while potentially less harmful sources of cannabis including tinctures and edible forms will no longer be accessible (Canadian Association of Medical Cannabis Dispensaries, 2013).

Given the historical reluctance of some physicians to authorize PLWHA to access CTP, reported barriers to access MMAP by CTP users and current policy shifts to alter the Government of Canada’s role in CTP, we sought to determine explanatory correlates of receiving
access to CTP in a population of PLWHA. While surveys of PLWHA based on relatively small sample sizes have outlined some of the demographic and symptom management details about medicinal cannabis users, to date few studies have examined the demographic, clinical and contextual factors associated with receiving a prescription for medical cannabis. In addition, very little research has examined the prevalence of being prescribed cannabis, explanatory correlates of prescribed cannabis use of PLWHA. As such, more research is required to determine what clinical and demographic characteristics’ are associated with prescribed cannabis use, and the safety of cannabis in this population.

1.2 Purpose of the Study

The primary purpose of this study was to determine whether an association exists between high-intensity or greater than daily cannabis use and adherence to ART in a population of PWID who are HIV-positive. Despite the evidence to support the efficacy of cannabis in the amelioration of HIV related symptoms, the evidence regarding cannabis use and the impact on adherence remains limited. To date, no long-term prospective studies assessing high-intensity cannabis use as a factor that may affect adherence have been conducted within a setting of universal healthcare where access to ART and HIV treatment is without user fees. The present study investigated the role of high-intensity or greater than daily cannabis use among a cohort of PWID, to determine if daily cannabis use was detrimental to ART adherence.

A secondary goal of this study was to identify the prevalence and correlates of being prescribed cannabis among a cohort of HIV-positive PWID living in Vancouver, British Columbia. Further, this study examined the rates of cannabis use for HIV-related symptoms among those who are and who are not prescribed cannabis. The study aims to add to the growing body of research on the prevalence, correlates and impact of cannabis use in PLWHA. In
particular, the study aims to describe high–intensity cannabis use and the association with adherence to HAART in a population of PWID where access to ART is free and cannabis is accessible with a prescription from a healthcare practitioner. The study was guided by the following questions:

1. What is the prevalence and demographic, clinical and structural correlates of high-intensity cannabis use in PLWHA PWID?

2. What is the longitudinal association between high intensity cannabis use and HAART adherence in PLWHA who are PWID?

3. What are the demographic, clinical and structural explanatory correlates associated with receiving a prescription for cannabis within PLWHA population of PWID?
Chapter 2: Research Methods

The following chapter describes the research methods utilized for both analyses.

2.1 Sample

Data for this study was obtained from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an ongoing observational prospective cohort of over 900 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 to determine CD4 count and HIV-1 viral load, participate in a nurse-administered questionnaire and physical 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 University of British Columbia and Providence Healthcare Research Ethics Board. Prior to the baseline interview, participants were asked to read through the consent form and then a research staff member reviewed the form and explained each detail of the consent to participants, to ensure informed consent took place. Participants are also given the option of withdrawing their participation from the study at any point. Due to the sensitive subject matter discussed in the questionnaire, and to help mitigate the potential for discomfort and stress to participants during the interview, it is explained to participants they have the option of not answering questions if they create undue stress during the interview.
2.2 Data Collection

At baseline and semi-annually, participants consent to participate in self-report interviews with trained interviewers and provide blood samples for CD4+ count, viral load, resistance and genotype testing. Two standardized interviewer-administered questionnaires are provided to the participants. One instrument elicits demographic data, information about drug use and sexual practices, exposures to the criminal justice and healthcare systems. A second interview, performed by a registered nurse, focuses on health-related outcomes including healthcare access and utilization, HIV management, and additional questions related to cannabis use. Most behavioural and health related outcomes recorded refer to the previous six month time period. In addition to the interviews, participants are examined by the nurse and provide blood samples for serological analysis. Participants are given a stipend ($20 CDN) at each study visit. 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., 2003a). The BC-CfE runs a centralized ART 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 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 British Columbia, allowing analysis of adherence to treatment free of the confounding influence of the cost of medications and HIV care.
2.2.1 Data Measurement for ‘High Intensity Cannabis Use and Adherence to ART’

The main study outcome, adherence to prescribed ART, was based on pharmacy refill data 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 versus 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., 2003b; Wood et al., 2003c).

This study included all ACCESS participants who were exposed to ART, had a baseline CD4+ and viral load 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 the self-report of at least daily cannabis use, in the previous six month period preceding the follow-up interview.

In order to estimate the relationship between high intensity cannabis use and adherence to ART, a number of explanatory variables were identified as possibly confounding this relationship, including; age, gender (female/male), Aboriginal ancestry (yes/no), educational attainment (< high school diploma/≥ high school diploma or greater) and formal employment in the previous six months (yes/no). The formal employment variable was defined, as in previous studies (Richardson et al., 2010), as having a regular job with a salary or temporary work in the six-month period prior to the interview. Individual and illicit drug use variables included; methadone maintenance therapy (yes/no), frequent cocaine injection (≥ daily/ < daily), frequent heroin injection (≥ daily/ < daily), frequent crack inhalation (≥ daily/ < daily), daily binge alcohol
use (>4 drinks per day (yes/no)) and binge drug use (yes/no). The Center for Epidemiological studies Depression scale (CES-D) was used to measure depression. The variable was dichotomized (scores ≥16/≤16) with individuals who scored greater than 16 considered to be 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 et al., 2000b; Radloff, 1977).

Clinical variables identified as potential confounders 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), ART regimen contains a protease inhibitor (PI) (yes/ no), and HIV experience of the prescribing physician (<six patients/≥ 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 enrolled in the province-wide HIV treatment registry at the time of ART initiation for the participant. Because the type of ART medications utilized may influence the presence of side effects and subsequently, impact adherence as well as the need for cannabis for symptom management, this variable is included in the analyses. Blood plasma HIV-1 RNA was measured using the Roche Amplicor Monitor Assay, a clinically proven and reliable method of viral load testing (Erali & Hillyard, 1999).

Additional structural variables found to influence ART adherence in similar populations were also included in the analysis as possible confounders. This included the variables 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/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/no).

2.2.2 Data Measurement for Prevalence and Explanatory Correlates of Receiving a Prescription for Cannabis

The secondary outcome, receiving a prescription for cannabis, was based on self-report answers to the question “Have you been prescribed medical cannabis in the past six months?” and further dichotomized into “yes” or “no”. The cross sectional perspective was based upon the first available observation per subject in ACCESS follow-ups numbered 12 and 13, which occurred between November 4th, 2011 and December 1st, 2012 when the cannabis prescription item was first introduced into the questionnaire. If a subject answered the question in follow-up 12 the results were retained for the analysis, and the results of follow-up 13 were then discarded.

In order to identify the explanatory correlates of being prescribed medical cannabis a number of variables hypothesized to be associated with the outcome were considered, including age (per year older), gender (female/male), Aboriginal ancestry (yes/no) and educational attainment (<high school diploma/≥high school diploma). Individual and illicit drug use variables included frequent crystal methamphetamine use (≥daily/<daily), frequent cocaine injection (≥daily/<daily), frequent heroin injection (≥daily/<daily), frequent crack inhalation (≥daily/<daily) and cannabis use (any/none). Additional individual, clinical and behavioural variables we hypothesized might influence access to care, prescriber patterns and be associated with the outcome included homelessness (yes/no), incarceration (yes/no), participation in sex work in the past six months (defined as any sexual acts in exchange for money, drugs, or other goods or favours) (yes/no), any treatment for drug/alcohol use in the past 6 months (yes/no), use of marijuana to manage HIV symptoms in the past 6 months (yes/no), requested pain
medications in the past six months (yes/no), ever been prescribed ART (yes/no), experienced barriers to health care (any response except “no barriers” or “myself” vs. no), difficult to get an HIV specialist doctor (yes/no). Clinical variables included CD4+ cell count and plasma HIV-1 RNA level. Blood plasma HIV-1 RNA was measured using the Roche Amplicor Monitor Assay, a clinically proven and reliable method of viral load testing (Erali & Hillyard, 1999).

2.3 Data Analysis for High Intensity Cannabis Use and Adherence to ART

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

Next, bivariate and multivariate generalized linear mixed-effects analyses were performed 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, a multivariate model was constructed that was 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. This variable was removed from the model and we 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 modeling strategy has been utilized previously to 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).

2.4 Data Analysis for Explanatory Correlates of Receiving a Prescription for Cannabis

As an initial step, we examined all the prevalence and percentages of all explanatory variables included in the analyses, stratified by the primary outcome being prescribed medical cannabis. This analysis included selected demographic (i.e., age, gender, Aboriginal ancestry, education), behavioural (i.e., at least daily drug use including, injection heroin, injection cocaine, crack cocaine and crystal methamphetamine) individual, risk, social and structural factors (i.e., participation in sex work, homelessness, incarceration, use of cannabis to manage HIV symptoms, requested pain medications, ever been prescribed ART, ever experienced barriers to health care, difficult to get an HIV GP) and clinical (i.e., HIV-1 viral load, CD4+ cell count) characteristics among those who did and did not report getting a prescription to cannabis in the previous 6 months. Next, based on these results, we then examined bivariate associations of receiving a prescription with odds ratios and 95% confidence intervals and p-values through use of chi-square estimations for categorical variables and Pearson's $\chi^2$ for continuous variables.
Chapter 3: Study Results

3.1 Results of Analysis of High-intensity Cannabis Use and Adherence to ART

Between May 2005 and April 2012, a total of 523 individuals that 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. At baseline, 248 (47.5%) participants reported any cannabis use in the past six months. Of these individuals, 121 (23.2%) participants reported at least daily cannabis use. Detailed baseline prevalence and frequency of cannabis use are presented in Table 1.

Table 1: Baseline prevalence of cannabis use of 523 ART-exposed illicit drug users in the last six months

<table>
<thead>
<tr>
<th>Frequency of Cannabis Use</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cannabis use(^1,(^2)</td>
<td>248 (47.5%)</td>
<td>274 (52.5%)</td>
</tr>
<tr>
<td>At least monthly cannabis use(^1)</td>
<td>237 (45.3%)</td>
<td>286 (54.7%)</td>
</tr>
<tr>
<td>At least weekly cannabis use(^1)</td>
<td>202 (38.6%)</td>
<td>321 (61.4%)</td>
</tr>
<tr>
<td>At least daily cannabis use(^1,(^2)</td>
<td>121 (23.2%)</td>
<td>401 (76.8%)</td>
</tr>
</tbody>
</table>

1. Refers to six-month period prior to interview
2. These variables had one missing response

The baseline characteristics of the sample stratified by at least daily cannabis use are presented in Table 2. At baseline, compared to less than daily cannabis users, at least daily cannabis users were: younger (44.2 years versus 46.6 years, \(p=0.002\)); more likely to be male (17.8% versus 5.36%, \(p<0.001\)); more likely to not have completed high school (14.7% vs. 8.4%, \(p=0.04\)); and more likely to drink more than four alcohol drinks daily (15.7% vs. 7.5%, \(p=0.004\)).
Table 2: Baseline characteristics of 523 ART-exposed illicit drug users stratified by at least daily cannabis use in the last six months, ACCESS study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Less than daily cannabis use</th>
<th>At least daily cannabis use</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 402 (76.9)</td>
<td>N = 121 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>46.6 (40.1 – 50.2)</td>
<td>44.1 (37.8 – 48.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>241 (60.1)</td>
<td>93 (76.9)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>160 (39.9)</td>
<td>28 (23.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Aboriginal ancestry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>252 (62.7)</td>
<td>77 (63.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>150 (37.3)</td>
<td>44 (36.4)</td>
<td>0.849</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; HS diploma</td>
<td>214 (53.2)</td>
<td>77 (63.6)</td>
<td></td>
</tr>
<tr>
<td>≥ HS diploma</td>
<td>188 (46.8)</td>
<td>44 (36.4)</td>
<td>0.043</td>
</tr>
<tr>
<td>Employment†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>339 (84.3)</td>
<td>104 (85.9)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63 (15.7)</td>
<td>17 (14.1)</td>
<td>0.663</td>
</tr>
<tr>
<td>DTES resident†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>197 (49.0)</td>
<td>68 (56.2)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>205 (51.0)</td>
<td>53 (43.8)</td>
<td>0.165</td>
</tr>
<tr>
<td>MMT, current†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>204 (50.8)</td>
<td>69 (57.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>198 (49.2)</td>
<td>52 (42.9)</td>
<td>0.225</td>
</tr>
<tr>
<td>Alcohol use†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 drinks/day</td>
<td>323 (80.3)</td>
<td>82 (67.8)</td>
<td></td>
</tr>
<tr>
<td>≥ 4 drinks/day</td>
<td>79 (19.7)</td>
<td>39 (32.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Heroin injection†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Daily</td>
<td>345 (85.8)</td>
<td>103 (85.1)</td>
<td></td>
</tr>
<tr>
<td>≥ Daily</td>
<td>57 (14.2)</td>
<td>18 (14.9)</td>
<td>0.847</td>
</tr>
<tr>
<td>Cocaine injection†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Daily</td>
<td>365 (90.8)</td>
<td>110 (90.9)</td>
<td></td>
</tr>
<tr>
<td>≥ Daily</td>
<td>37 (9.2)</td>
<td>11 (9.1)</td>
<td>0.969</td>
</tr>
<tr>
<td>Crack cocaine use†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Daily</td>
<td>244 (60.7)</td>
<td>80 (66.1)</td>
<td></td>
</tr>
<tr>
<td>≥ Daily</td>
<td>158 (39.3)</td>
<td>41 (33.9)</td>
<td>0.281</td>
</tr>
<tr>
<td>Binge drug use†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>315 (78.4)</td>
<td>101 (83.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>87 (21.6)</td>
<td>20 (16.5)</td>
<td>0.221</td>
</tr>
<tr>
<td>Adherence†</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3 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 use and ART adherence in a bivariate analysis (Odds Ratio [OR] = 0.91; 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. 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 3. After adjustment for viral load, 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.
Table 3: Longitudinal bivariate and multivariate mixed-effects analyses of factors associated with ≥95% adherence to ART in the previous six months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR(^1)</th>
<th>95% CI(^2)</th>
<th>p-value</th>
<th>AOR(^3)</th>
<th>95% CI(^2)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis use (≥daily vs. less)(^4)</td>
<td>0.91</td>
<td>0.63 – 1.30</td>
<td>0.618</td>
<td>1.12</td>
<td>0.76 – 1.64</td>
<td>0.555</td>
</tr>
<tr>
<td>Age (per year older)</td>
<td>1.07</td>
<td>1.04 – 1.10</td>
<td>&lt; 0.001</td>
<td>0.98</td>
<td>0.95 – 1.01</td>
<td>0.351</td>
</tr>
<tr>
<td>Gender (Female/male)</td>
<td>0.57</td>
<td>0.37 – 0.88</td>
<td>0.010</td>
<td>0.76</td>
<td>0.51 – 1.13</td>
<td>0.186</td>
</tr>
<tr>
<td>Aboriginal ancestry (Yes/no)</td>
<td>0.50</td>
<td>0.32 – 0.76</td>
<td>0.701</td>
<td>0.70</td>
<td>0.47 – 1.03</td>
<td></td>
</tr>
<tr>
<td>Homeless (Yes/no)</td>
<td>0.44</td>
<td>0.28 – 0.71</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (≥HS diploma/&lt; HS diploma)</td>
<td>1.14</td>
<td>0.75 – 1.74</td>
<td>0.515</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol (≥4 drinks/&lt;4 drinks)(^4)</td>
<td>0.69</td>
<td>0.50 – 0.94</td>
<td>0.021</td>
<td>0.82</td>
<td>0.58 – 1.16</td>
<td>0.276</td>
</tr>
<tr>
<td>CM injection (≥daily/&lt;daily)(^4)</td>
<td>0.58</td>
<td>0.20 – 1.67</td>
<td>0.316</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin injection (≥daily/&lt;daily)(^4)</td>
<td>0.33</td>
<td>0.21 – 0.49</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine inject (≥daily vs less)(^4)</td>
<td>0.62</td>
<td>0.40 – 0.95</td>
<td>0.027</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crack use (≥daily vs less)(^4)</td>
<td>0.49</td>
<td>0.37 – 0.65</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incarceration (Yes/ no)(^4)</td>
<td>0.54</td>
<td>0.36 – 0.82</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMT (Yes/ no)</td>
<td>2.65</td>
<td>1.91 – 3.68</td>
<td>&lt; 0.001</td>
<td>1.49</td>
<td>1.08 – 2.06</td>
<td>0.015</td>
</tr>
<tr>
<td>CESD score (≥16 vs &lt;16)</td>
<td>0.98</td>
<td>0.70 – 1.35</td>
<td>0.902</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment (Yes/ no)(^4)</td>
<td>1.25</td>
<td>0.86 – 1.73</td>
<td>0.254</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since HIV (per month)</td>
<td>1.00</td>
<td>0.99 – 1.00</td>
<td>0.954</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regimen includes PI (Yes/no)</td>
<td>11.71</td>
<td>8.30 – 16.5</td>
<td>&lt; 0.001</td>
<td>6.41</td>
<td>4.62 – 8.88</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CD4+ cells (Per 100 cells/mm(^3))</td>
<td>1.51</td>
<td>1.37 – 1.65</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma HIV RNA/mm(^3) (log10)</td>
<td>0.34</td>
<td>0.30 – 0.38</td>
<td>&lt; 0.001</td>
<td>0.36</td>
<td>0.37 – 0.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HIV MD (≥ 6 patients vs less)</td>
<td>1.60</td>
<td>0.98 – 2.86</td>
<td>0.057</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Odds Ratio
2. 95% Confidence Interval
3. Adjusted Odds Ratio
4. Refers to the six month period prior to the interview
3.2 Results of Analyses of Explanatory Correlates of Receiving a Prescription for Cannabis

Between April 2012 and December 2012, 519 individuals were included in the study. In the analytical sample, 183 (35.2%) participants were female and 218 (42%) participants reported Aboriginal ancestry. In the cross-sectional analysis, 81 (15.6%) individuals reported receiving a prescription for cannabis in the past 6 months.

Demographic, clinical and individual characteristics of the sample, stratified by those receiving a prescription for cannabis are presented in Table 4.

Table 4: Cross-sectional and bivariate analyses of explanatory correlates of receiving a prescription for cannabis in the previous six months, among 519 participants in the ACCESS study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No prescription for cannabis (n= 438)</th>
<th>Received a prescription for cannabis (n=81 )</th>
<th>OR^2</th>
<th>95% CI</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year older)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>47.1 (40.8-52.4)</td>
<td>47.1 (41.8-50.9)</td>
<td>0.99</td>
<td>0.97 – 1.03</td>
<td>0.942</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>270 (61.6)</td>
<td>66 (81.5)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>168 (38.4)</td>
<td>15 (18.5)</td>
<td>0.375</td>
<td>0.20 – 0.68</td>
<td>0.0012</td>
</tr>
<tr>
<td>Aboriginal ancestry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>253 (57.8)</td>
<td>48 (59.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>185 (42.2)</td>
<td>33 (40.7)</td>
<td>0.90</td>
<td>0.55 – 1.47</td>
<td>0.682</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥HS diploma</td>
<td>202 (46.1)</td>
<td>38 (46.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; HS diploma</td>
<td>211 (48.2)</td>
<td>37 (45.7)</td>
<td>0.93</td>
<td>0.57 – 1.52</td>
<td>0.779</td>
</tr>
<tr>
<td>Unstable housing^1,4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>174 (39.7)</td>
<td>41 (50.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>250 (57.8)</td>
<td>39 (48.2)</td>
<td>0.66</td>
<td>0.41 – 1.07</td>
<td>0.091</td>
</tr>
<tr>
<td>Sex work^1,4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>400 (91.3)</td>
<td>78 (96.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (6.6)</td>
<td>2 (2.4)</td>
<td>0.35</td>
<td>0.08 – 1.51</td>
<td>0.161</td>
</tr>
<tr>
<td>Addiction treatment^1,4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>187 (42.7)</td>
<td>39 (48.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>239 (54.6)</td>
<td>40 (49.4)</td>
<td>0.80</td>
<td>0.49 – 1.29</td>
<td>0.369</td>
</tr>
</tbody>
</table>

Any Cannabis use^1,4
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No prescription for cannabis (n=438)</th>
<th>Received a prescription for cannabis (n=81)</th>
<th>OR^2</th>
<th>95% CI^2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>289 (65.9)</td>
<td>21 (25.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>140 (32.0)</td>
<td>59 (72.8)</td>
<td>5.80</td>
<td>3.39 – 9.93</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cannabis use for HIV symptoms(^1,4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>336 (76.7)</td>
<td>17 (20.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>102 (23.3)</td>
<td>64 (79.1)</td>
<td>12.37</td>
<td>6.93 – 22.06</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Requested a prescription for pain medications(^1,4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>268 (61.2)</td>
<td>50 (61.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>168 (38.4)</td>
<td>31 (38.3)</td>
<td>0.98</td>
<td>0.61 – 1.61</td>
<td>0.964</td>
</tr>
<tr>
<td>Barriers to accessing healthcare services(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>377 (86.1)</td>
<td>68 (83.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (13.9)</td>
<td>13 (16.1)</td>
<td>1.18</td>
<td>0.62 – 2.27</td>
<td>0.616</td>
</tr>
<tr>
<td>Difficult to find an HIV GP(^1,4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>390 (89.0)</td>
<td>69 (85.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47 (10.8)</td>
<td>10 (12.3)</td>
<td>1.20</td>
<td>0.58 – 2.49</td>
<td>0.619</td>
</tr>
<tr>
<td>Incarceration(^1,4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>412 (94.06)</td>
<td>76 (93.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (2.97)</td>
<td>3 (3.7)</td>
<td>1.25</td>
<td>0.35 – 4.49</td>
<td>0.731</td>
</tr>
<tr>
<td>Heroin injection(^1,4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Daily</td>
<td>390 (89)</td>
<td>76 (93.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Daily</td>
<td>36 (8.2)</td>
<td>4 (4.9)</td>
<td>0.57</td>
<td>0.19 – 1.65</td>
<td>0.299</td>
</tr>
<tr>
<td>Cocaine injection(^1,4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Daily</td>
<td>404 (92.2)</td>
<td>75 (92.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Daily</td>
<td>22 (5.0)</td>
<td>5 (6.2)</td>
<td>1.22</td>
<td>0.45 – 3.33</td>
<td>0.692</td>
</tr>
<tr>
<td>Crack cocaine inj(^1,4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Daily</td>
<td>344 (78.5)</td>
<td>70 (86.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Daily</td>
<td>82 (18.7)</td>
<td>9 (11.1)</td>
<td>0.53</td>
<td>0.26 – 1.12</td>
<td>0.099</td>
</tr>
<tr>
<td>Crystal Meth inj(^1,4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Daily</td>
<td>423 (96.6)</td>
<td>79 (97.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Daily</td>
<td>6 (1.3)</td>
<td>1 (1.23)</td>
<td>0.89</td>
<td>0.11 – 7.51</td>
<td>0.916</td>
</tr>
<tr>
<td>CD4+ cell count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.04 (2.6 - 5.4)</td>
<td>3.8 (2.6 - 5.5)</td>
<td>0.99</td>
<td>0.89 – 1.10</td>
<td>0.889</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.5 (1.5 - 2.4)</td>
<td>1.5 (1.5 - 2.4)</td>
<td>0.96</td>
<td>0.78 – 1.19</td>
<td>0.738</td>
</tr>
</tbody>
</table>

1. Refers to six month period prior to interview
2. Odds Ratio
3. 95% Confidence Interval
4. These variables had a small number of missing values
Cross-sectional bivariate analyses of explanatory correlates of receiving a prescription for cannabis in the previous six months are presented in Table 4. Using cannabis in the past 6 months (odds ratio [OR] = 5.80; 95% CI: 3.39-9.93, \( p < 0.001 \)) and using cannabis for HIV symptom management (OR = 12.37; 95% CI: 6.93-22.06, \( p < 0.001 \)) were positively associated with receiving a prescription for cannabis. Female gender (OR = 0.37; 95% CI: 0.20–0.68, \( p=0.0012 \)) was negatively associated with receiving a prescription for cannabis.
Chapter 4: Conclusion

In the conclusion section the implications and limitations for each analysis will be discussed separately.

4.1 Discussion of the Results: Analysis of High-intensity Cannabis Use and Adherence to ART

In this longitudinal study of ART-exposed PWID, we found high intensity cannabis use was not associated with sub-optimal adherence in PLWHA. We did not find evidence that daily or more frequent cannabis use compromises effective HIV adherence. This is significant as it has been previously shown that HIV-infected PWID who are able to achieve adherence levels ≥95% are able to derive the clinical benefits of HIV-1 RNA viral suppression and CD4+ cell count increases (Wood et al., 2003b; Wood et al., 2003c).

The findings related to the prevalence of cannabis use at baseline are in line with other studies examining cannabis use in PLWHA populations where 17-59% of PLWHA report cannabis use. Almost half of the cohort, or 47.5%, reported cannabis use in the past 6 months, with 45.3% reporting monthly use; 38.6% reporting using every week; and 23.4% reporting at least daily use. Given the high percentage of weekly and daily usage described here, healthcare practitioners should be routinely screening PLWHA clients for cannabis use and discussing possible harm reduction methods of cannabinoid use, such as oral tinctures, oral mucosal sprays, edible forms of cannabis and the use of vaporizers that may reduce the impact to their respiratory health (Abrams et al., 2007b). Healthcare practitioners may also wish to direct clients to community-based dispensaries, which offer oral forms of cannabis in the guise of baked goods, tinctures and some organic cannabis products (i.e., free from pesticides and herbicides) to clients for medical purpose with the authorization of a physician. CTP users have previously identified
a preference for cannabis to be produced organically and oral forms of cannabinoids to be made available (Lucas, 2012). While the community-based dispensaries remain an illegal source of cannabis products, they provide a safer source of cannabis than other illegal or street-based suppliers and are frequently identified by CTP users as a preferred source for cannabis products (Lucas, 2012). The dispensaries have recently moved towards standardization and continue to provide education that supports decision-making and informed patient choice about cannabis (CAMCD, 2013).

The lack of association between cannabis use and adherence found in this research is congruent with a number of studies conducted amongst PLWHA. An observational 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, however, adherence was negatively associated with illicit drug use and alcohol (de Jong et al., 2005). In other observational studies among convenience samples of PLWHA in Canada and the US, 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 actually 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.

There are, however, a few studies that contradict our findings and 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 HIV- related symptoms (Bonn-Miller, Oser, Bucossi, & Traffton, 2012). The authors, however, 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. This study was also limited by self-reported adherence measures, with inconsistencies reported between short-term and longer term self-report adherence rates. In a study of 775 PLWHA from Africa, Puerto Rico and the US 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 study of 200 PLWHA based in Australia, found that participants who reported cannabis use greater than 4 times per week had an increased likelihood of poor adherence to ART (Wilson, Doxanakis, & Fairly, 2004). However, it should be noted that all of these studies are likely limited by their cross-sectional nature and the limited number of possible confounding variables included in their analyses. In addition, in all of these studies adherence was measured by self-report, which has been found to be of limited validity (Kerr, Walsh, Lyoyd-Smith & Wood, 2005b: Kerr et al., 2008). In contrast, our study 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 viral load. Further, we are unaware of any other analysis to date that has examined high intensity cannabis use and adherence to ART longitudinally in a population of PWID who have free medication and healthcare access.

4.1.1 Practice and Policy Implications

Despite improved legal access to cannabis for PLWHA 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), many healthcare practitioners remain reluctant to prescribe cannabis to patients (Belle-Isle & Hathaway, 2007). Healthcare practitioners may have concerns about safely prescribing cannabis when its psychoactive effects
including mental confusion and memory impairment, may impact the patient’s ability to safely adhere to their medications. While our study did not analyze adherence and memory impairment or address the safety of prescribing cannabis, our findings suggest daily cannabis use may not compromise effective adherence to ART. Prescribing physicians may wish to exercise caution when prescribing to individuals with existing CNS disturbances, like HAND, until further studies can examine how adherence is impacted by cannabis use in these groups.

There also may be concerns amongst practitioners related to cannabis being utilized for recreational or non-intended purposes and potential for psychological addiction with chronic use (Zvolensky et al., 2011). It should be noted that psychological addiction to cannabis has not been well established and that CTP users do not consider addiction to cannabis to be a priority (Bottorff et al., 2012). Concerns about cannabis misuse in a population with a history of illicit drug use should be examined within the context of effective symptom management, and addiction to other illicit drugs, which create greater self-harm and additional public health issues. However, such studies should also consider whether cannabis use in this population has potential to offset more problematic forms of illicit drug use. While concerns regarding inappropriate use and abuse 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, the development of educational materials for healthcare practitioners that address the potential harms of cannabis in the context of larger social issues faced by PLWHA would be beneficial.

We did not examine the impact of cannabis use for medical purposes on symptom management in PLWHA and ART adherence, which has been previously been 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 addition, given that memory deterioration has been identified as a common side effect of cannabis use (Woolbridge et al., 2005) and HAND is commonly experienced by PLWHA with more advanced HIV, further studies should examine the impact of frequent cannabis use, memory impairment and ART adherence amongst PLWHA who are experiencing neurocognitive deterioration. Given the high incidence of daily and weekly cannabis use in the sample, additional research examining the potential interactions between ART medications, HIV and immunological function and cannabis use should be conducted to determine the safety of frequent cannabis use within PLWHA.

Healthcare practitioners may also consider providing additional information about potential adverse effects of cannabis use previously identified within PLWHA populations including memory impairment, euphoria, dry mouth, drowsiness, paranoia, heart palpitations and anxiety. In particular, healthcare practitioners should highlight potential benefits and side effects to patients who are naïve to cannabis, those with existing mental health conditions, and those individuals they believe may be adversely affected by cannabis use.

Practitioners may also have concerns about the long term use of smoked cannabis. While the evidence associating long-term cannabis smoking and respiratory diseases is unclear, respiratory dysfunction has been reported amongst high-intensity or daily cannabis smokers (Kalant, 2004). In light of these concerns, practitioners might encourage cannabis smokers to utilize vaporization devices, which have been found to deliver THC without some of the harms associated with smoked cannabis (Abrams et al., 2007b).
4.1.2 Strength and Limitations

The analysis of the impact of cannabis use on adherence to ART had several limitations. As a secondary analysis of a pre-existing data base, the analysis was limited to the study variables already included in the questionnaire. While we attempted to control for a number of potentially confounding variables, adherence to ART is extremely complex and we cannot exclude the possibility that confounding variables were not included in the analysis. In addition, there was a small percentage, less than 5% for each variable, of missing data excluded from the data set. We do not believe the exclusion of this data influenced the outcomes and analyses in the multivariate model. In addition, the measure for depression may face some specific limitations - 78 of the respondents did not provide an answer for the scale. These non-responders were fairly balanced within the adherent (n=43) and non-adherent groups (n=35) and, therefore it is unlikely the exclusion of these responses affected the association between high-intensity cannabis use and adherence to ART in the multivariate analyses. Secondly, it is possible that severely depressed people were not motivated to answer this portion of the questionnaire and this may have influenced the results for this particular variable. While the CES-D has previously been validated as a reliable and acceptable tool for assessing depressive symptoms, it may overestimate the number of depressed individuals as often those individuals who self-report depressive symptoms fail to meet the criteria for clinical depression (Williams et al., 2002).

A number of the study variables may be vulnerable to self-report bias, as participants may be reluctant to answer candidly to questions related to drug use or mental illness, for fear of stigma associated with these. In addition, memory recall may also limit the validity of self-report responses. We also utilized a cohort with a history of illicit drug use who live in a setting where access to ART medications and HIV care is free. As such, the study findings may be limited to
these individuals and not generalizable to different populations in other geographic areas and health care systems.

Another limitation of our study, as the routes of administration and variability of cannabis strains can impact the amount of cannabinoids ingested by individual participants, we could not control or account for how this may have influenced adherence and cannabis use generally in the population.

The pharmacy refill measure used as a proxy to ART adherence may overestimate adherence in the sample, as it indicates the number of ART prescriptions refilled without capturing the actual ingestion of these medications. However, this measure has previously been proven to be an accurate predictor of virological suppression (Wood et al., 2003c).

There are a number of strengths in the study. The study involved a large community recruited longitudinal cohort allowing for the inclusion of data from a number of time points and variability in the responses over time. Trained interviewers also administered the questionnaires, increasing the reliability of the data. The study included a large number of potentially confounding variables, previously identified to influence ART adherence among PWID populations. We also utilized a proven measure of adherence, pharmacy refill data, which has been shown to be an accurate predictor of virological suppression and survival.

4.2 Discussion of the Results: Analysis of Explanatory Correlates of Receiving a Prescription for Cannabis

Less than one-fifth (15.8%) of participants in the sample reported obtaining a prescription for cannabis in the previous six months. Of those who reported obtaining a prescription, 64 (79.1%) indicated they had used cannabis to manage HIV symptoms in the past 6 months. In addition, of the 166 PLWHA in the sample who reported cannabis use to manage HIV symptoms
in the previous 6 months, 64 (38.5%) reported they were able to obtain a prescription for cannabis in the previous 6 months. This finding is similar to an earlier assessment of PLWHA accessing CTP in Canada, which found 33.8% of PLWHA who reported medicinal cannabis use had applied for legal access, with the majority of PLWHA accessing through other means (Belle-Isle & Hathaway, 2007). Previous research has also identified that a number of PLWHA experienced difficulty accessing CTP through their physician (Belle-Isle & Hathaway, 2007). In addition PLWHA who use CTP also reported experiencing stigma from health care practitioners related to their CTP use (Bottorff et al., 2012). While it is difficult to assess if participants experienced any difficulty accessing support from their physicians related to obtaining a prescription for CTP, these results suggest at least a third of PLWHA do seek legally sanctioned cannabis to help manage their HIV symptoms.

The bivariate results indicate cannabis use for HIV symptom management was positively associated with receiving a prescription for cannabis, suggesting cannabis use for HIV symptom management continues to motivate a large number of PLWHA to obtain legal access. Alternatively, requests for CTP prescriptions by PLWHA with significant symptoms are more likely to be supported by physicians than those with less severe symptoms.

The PLWHA who report CTP use for HIV symptom management also represent a significant majority of the cannabis users in the study, with 166 (83.4%) of those who reported any cannabis use (n=199) in the previous 6 months reporting cannabis use to manage HIV-related symptoms. These findings are in line with a number of previous studies that have found positive associations between cannabis use and HIV symptom management in PLWHA populations (Woolridge et al., 2005; de Jong et al., 2005; Furler et al., 2004; Ware et al., 2003;
Prentiss et al., 2003). The continued use of CTP by PLWHA for HIV symptom management reinforces the assertion that cannabis is an effective medication for the treatment of HIV-related symptoms and management of HIV disease. Further, randomized trials of cannabis and cannabinoids are also needed to fully understand their role in HIV symptom management and disease processes.

The finding that female gender was negatively associated with obtaining a prescription for cannabis suggests there may be some barriers to women accessing a prescription for cannabis. While it is difficult to discern the exact nature of this relationship, there are a number of possibilities. It may be that women are facing additional stigma and experiencing greater difficulty accessing cannabis from their physician. Fear of stigma from health care practitioners may influence women from asking for a prescription for CTP. Additional qualitative research examining women’s access to CTP may be helpful in identifying the exact nature of this phenomenon and if women are experiencing barriers to accessing CTP.

4.2.1 Strength and Limitations

This study has some limitations. Firstly as a cross-sectional perspective, it is difficult to discern if prescribing practices are being impacted over time and in particular by the recent changes in the MMAR regulations. As previously outlined, physician groups have expressed reservations about their expanded role under the new regulations, in particular the removal of Health Canada having final approval of MMAR licensing (CMA, 2013). Future research that examines prescribing practices and characteristics of those receiving a prescription over time, may be beneficial in identifying how the recent changes to the MMAR are impacting access to legal cannabis. Secondly, the outcome variable of receiving a prescription for cannabis may be
subject to a self-report bias. In addition, because individuals can receive access to cannabis from cannabis dispensaries with a document signed by their physician, it is unclear whether these individuals would have identified themselves as receiving a prescription for cannabis, without actually applying for access via the MMAR and receiving a Health Canada exemption. Future studies examining legal cannabis access in PLWHA populations, may provide a clearer picture of this phenomena and its correlates by limiting the question to those who have received Health Canada exemption exclusively.

There was a small percentage, less than 5% for each variable, of missing data excluded from the data set for the bivariate analysis. We do not believe the exclusion of this data would influence the outcomes presented.

The study has a number of strengths. This was the first study which examined the correlates of receiving a prescription in past six months and included a large number of explanatory variables that may influence prescriber patterns. The study involved a long-standing community-recruited cohort of PLWHA and utilized trained interviewers.

4.2.2 Practice, Policy and Future Research

The recent changes to the MMAR announced June 19, 2013 and going into full effect March 31, 2014, will alter how PLWHA are currently accessing CTP. Under the new regulations doctors and nurse practitioners will now provide their patients with a ‘medical document’ or declaration that states the patient meets the Health Canada criteria for permitting access to CTP. The declaration also outlines the amount of cannabis the patient requires to treat their condition. Physician groups have been critical of prescribing cannabis like other medications and the new regulations contained in the MMAR, citing the lack of research on the safety of long-term cannabis use and concerns regarding the inability to standardize or control dosages related to a
variability of potency between cannabis strains and the route of administration (Leslie, 2013).

Physician groups had expressed concerns that by removing Health Canada approval they would be held responsible and potential liable as prescribers of medicinal cannabis. However, under the new regulations, the “medical document” will not provide doses or directions or imply the practitioner recommends or advises CTP users to ingest or smoke cannabis (Beaulieu, CFPC press release, 2013). While the creation of the ‘medical document’ may ease some of the concerns raised by physician groups about being held responsible for prescribing cannabis, it remains to be seen if practitioners and their governing bodies will support the changes to the MMAR, which may have a large impact on access to CTP. At the same time, access to CTP may improve as patients will no longer have to endure the lengthy process of obtaining Health Canada approval in addition to their practitioner support, which had been identified by MMAR applicants previously as a time-consuming barrier to obtaining CTP (Belle-Isle & Hathaway, 2007). Future studies that can compare access rates before and after the changes to the MMAR, will be helpful in identifying if the recent changes are impacting access.

Given the prevalence of those seeking a prescription and the number of PLWHA who report using cannabis for management of HIV-related symptoms found in this study, health practitioner organizations should encourage their membership to maintain a level of knowledge regarding the benefits of cannabis and CTP. Current education is available on-line for practitioners and the general public (CCIC, 2013). This type of CTP education may help reduce some of the stigma experienced by PLWHA in their interactions with healthcare practitioners and help practitioners provide advice to clients managing HIV symptoms with CTP.

There have also been concerns that changes to the MMAR will impact access to CTP by creating a financial barrier and limiting the availability of certain forms of cannabis. Under the
new legislation CTP users will be provided with “dried” cannabis from licensed producers (Health Canada, 2013). As such, orally ingested forms of cannabis (e.g., cannabis tinctures) and potentially less-harmful forms of cannabinoids will not be commercially available and potentially not legal. There have also been concerns raised about the potential for increased costs to consumers under the new regulations. The British Columbia Civil Liberties Union has suggested that changes to the MMAR will create a financial barrier for users with limited financial means (BCCLC, 2013). Under the new regulations cannabis cannot be produced in an in-dwelling unit and there is no limit to what producers can charge for their product. Courier costs to transport cannabis from producers to consumers will also be applied, which may also greatly increase the cost to consumers. These changes eliminate a CTP user’s ability to grow cannabis in their own home, which can be relatively inexpensive in comparison to purchasing from a registered commercial grower. These factors may result in significant increases in the cost of cannabis to PLWHA, potentially limiting access to those with a low-income. As a number of PLWHA are currently living on a fixed income, their ability to access cannabis via the MMAR may be severely restricted. If CTP users are forced to rely upon commercial producers, they may no longer be able to afford cannabis at their current consumption rates (BCCLC, 2013). These financial barriers may force CTP users to rely upon illegal sources of cannabis. Government policies need to account for the unique financial context of many PLWHA and take into account the financial limitations many PLWHA face. Future studies that examine cost to users, dependence on illegal sources and satisfaction with cannabis produced by commercial growers, will be helpful in identifying if financial or other barriers exist and if CTP users are benefiting by the changes to the MMAR.
4.2.3 Summary

In summary, we found almost a quarter (23.1%) of the ART-exposed PWID participants, were high-intensity 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. In addition, we found 15.8% of participants in the study reported receiving a prescription for cannabis in the study period and a majority of PLWHA surveyed identified their cannabis use was associated with HIV symptom management. Cannabis use and cannabis use for HIV-symptom management were positively associated with receiving a prescription, indicating a large number of PLWHA continue to access and benefit from legally sanctioned cannabis to help manage their HIV.

With the introduction of HAART and advancement of ART, HIV-related morbidity and mortality rates have continued to improve in PLWHA populations who are able to adhere to ART (Zwhalen et al., 2009). HIV is increasingly being experienced as a chronic illness, with PLWHA living longer but having to cope with HIV-related symptoms and ART side effects. PLWHA continue to utilize cannabis and other complementary associated medications to manage HIV-related symptoms and achieve a better quality of life. Health care practitioners and their organizations continue to be resistant to their role in granting access to CTP, often citing safety and prescribing concerns (Leslie, 2013; CMA, 2013). The results of this study, in particular the lack of association between adherence to ART and daily cannabis use, may help alleviate some concerns related to the safety of prescribing cannabis to PLWHA who are on ART. While there continue to be a number of unanswered safety concerns related to cannabis use among PLWHA, in particular long-terms effects of cannabis use, these concerns need to be
balanced with patient–centered approaches to HIV-symptom management. A number of
PLWHA who utilize CTP have identified facing stigma from health care professionals and the
general public related to their cannabis use (Bottoroff et al., 2012). Given the prevalence of
cannabis use for HIV-symptom management reported in this study, this is troubling. In addition,
PLWHA have also identified barriers to accessing CTP under the current MMAR, with
additional concerns raised about how the new MMAR regulations may also reduce access. As a
result of these barriers to legal cannabis supply, a large number of PLWHA continue to rely upon
illegal sources for cannabis. Moving forward, government agencies and healthcare practitioner
organizations need to incorporate cannabis education and patient-centered approaches in their
policies and practices regarding CTP. These changes may improve legal access by alleviating
stigma and barriers to CTP identified by PLWHA.
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