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Abstract Occasional cannabis use has been associated with increased antiretroviral therapy (ART) adherence and relief of HIV symptoms, while heavy use has been associated with low ART adherence and negative psychological symptoms. The purpose of the present study was to investigate differences between non-cannabis use (NC), non-dependent cannabis use (C), and dependent use (CD) in terms of ART adherence and HIV symptoms/ART side effects. A cross-sectional sample of 180 HIV+ individuals (78.3 % male) completed measures of substance use and psychopathology, medication adherence, and HIV symptoms/ART side effects. Adherence was also measured via pill count, viral load, and CD4 count. Results indicated that the CD group reported lower adherence and greater HIV symptoms/ART side effects than the other two groups, with no differences observed between NC and C groups. There is a clinical need to address dependent cannabis use among those prescribed ART. Further examination is needed to ascertain the functions of cannabis use among individuals with HIV.

Keywords Cannabis · Marijuana · HIV · Adherence · Symptoms · Side effects

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Introduction

Human immunodeficiency virus (HIV) is widely prevalent in the U.S., with approximately 1.1 million individuals estimated as infected with the virus (Centers for Disease Control and Prevention [CDC], 2012). Antiretroviral medication, the "gold standard" for treating HIV, has progressively improved and, if taken correctly, significantly extends lives and reduces mortality rates, transforming HIV into a chronic illness (Crum et al., 2006; Mocroft et al., 2003). Here, earlier research indicated that medication adherence of at least 95 % was required to achieve HIV viral suppression, lower hospitalization rates, as well as decreased burden of the infection and risk of virus transmission (Bangsberg et al., 2007; Haubrich et al., 1999; Paterson et al., 2000; Wood et al., 2004). While advances in pharmacotherapy have made antiretroviral medication regimens more manageable and may allow for positive outcomes with imperfect adherence in some patients (Amico et al., 2012), low adherence is associated with medication resistance, increased HIV viral load, risk of developing acquired immune deficiency syndrome (AIDS), and increased mortality (Paterson et al., 2000; Bangsberg et al., 2001; Gifford et al., 2000; Hogg et al., 2002).

Despite the medical advances in HIV care, suboptimal adherence to antiretroviral therapy (ART) remains common

with the average adherence rate across studies and groups hovering around 70 % (Machtinger and Bansberg, 2012). Studies that have assessed adherence rates among individuals with HIV have found that between 14 and 35 % of individuals with HIV have trouble maintaining at least 80 % adherence to ART (Chesney 2003; Solomon & Halkitis, 2008), with viral suppression not achieved among 30–70 % of HIV positive individuals (Paterson et al., 2000; Low-Beer et al., 2000). The primary contributors to poor adherence among individuals with HIV include medication side effects (e.g., nausea), regimen complexity (e.g., number of pills), substance use (French et al., 2011; Friedman et al., 2009), and emotional factors (e.g., anxiety, depression) (Beusterien et al., 2008; Parienti et al., 2009).

There is growing recognition that individuals with HIV report greater cannabis use than the general population. Studies examining rates of cannabis use among individuals with HIV suggest that between 23 % and 56 % of HIV + individuals have used cannabis in the past month (Hosek et al., 2005; Prentiss et al., 2004). For comparison, only 6.9 % of the general U.S. population over age 12 reported past month cannabis use in 2010 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2011). These rates are particularly noteworthy as, even in places where the use of cannabis for medicinal purposes is sanctioned, the large majority of cannabis using individuals with HIV (86 %) obtain their cannabis from illegal sources (Belle-Isle & Hathaway, 2007). Though some studies examining the negative effects (e.g., decreased cognitive functioning; Cristiani et al., 2004) of cannabis on individuals with HIV have been conducted, the literature pertaining to the use of cannabis among individuals with HIV has primarily focused on its positive effects (Corless et al., 2009). Here, studies have shown that approximately 25–33 % of individuals with HIV report using cannabis to alleviate HIV-related symptoms and medication side effects (Fogarty et al., 2007; Woolridge et al., 2005). Specifically, HIV + individuals report the primary benefits of cannabis use to be the (1) alleviation of anxiety and depression, (2) stimulation of appetite and resulting weight gain, and (3) relief of pain (Prentiss et al., 2004; Abrams et al., 2007; Furler et al., 2004; Haney et al., 2007).

Though there are many empirical studies on the effects of cannabis use on HIV symptoms/ART side effects, there is a general dearth of literature examining the effects of cannabis use on HIV treatment adherence. Because of the preliminary nature of these studies, there is no agreement as to the extent to which cannabis is beneficial or detrimental to adherence. As an illustrative example, cannabis use for the purpose of alleviating nausea was found to improve HIV treatment adherence (de Jong et al., 2005), while heavy cannabis use has been associated with non-adherence (Wilson et al., 2004). Other studies have found similar negative effects of cannabis use, more broadly, in terms of treatment adherence (Corless et al., 2009; Tucker et al., 2003). Specifically, in a study of a representative U.S. sample of 1,910 HIV + patients who self-reported on their antiretroviral adherence, Tucker et al., (2003) found patients with past-month cannabis use to be at increased odds of non-adherence to antiretroviral medication than non-users. Similarly, in a study by Corless et al., (2009) among 775 individuals with HIV from Africa, Puerto Rico, and the contiguous U.S., individuals who used cannabis had significantly poorer adherence than individuals who did not. A study of 200 Australians with HIV by Wilson et al., (2004) found that using cannabis more than 4 times per week was associated with increased odds of self-reported non-adherence (defined as less than 98.2 % adherence). These data collectively indicate that the interrelations between cannabis use and treatment adherence are complex, with differences in adherence likely involving functionally distinct cannabis use patterns.

Though there has been some empirical study of the effects of cannabis use on HIV treatment adherence, there has been no consistency in findings. Additionally, of the existing studies of the relations between cannabis use and HIV treatment adherence, none have classified cannabis use by diagnostic criteria (e.g., dependence), a more accurate method of identifying problematic use patterns. Indeed, as quantity of use as well as problems associated with use are central to understanding cannabis use patterns as well as intervention targets, the examination of frequency of use provides a poor metric of those severely impacted by cannabis use (Bonn-Miller & Zvolensky, 2009; Grant & Pickering, 1998). This lack of research focused expressly on the association between cannabis use patterns (beyond simply frequency of use) and antiretroviral treatment adherence, is particularly noteworthy. Such research is central for understanding risk for low treatment adherence among individuals with HIV.

The present study aimed to fill these clinically significant gaps in the HIV literature by exploring associations between cannabis use and ART adherence and HIV symptoms/ART side effects. The primary purpose of this project was to evaluate the extent to which non-cannabis use (NC) and dependent use (CD) was associated with suboptimal HIV treatment adherence and a heightened experience of HIV symptoms/ART side effects, as compared with non-dependent cannabis use (C). Indeed, we predicted a non-linear relation between cannabis use patterns (i.e., non-use, non-dependent use, and dependent use) and ART adherence and HIV symptoms/ART side effects, based on previous literature reporting benefits of cannabis for side-effect management.

Consistent with the HIV treatment adherence literature, we posited that non-cannabis using individuals would experience negative effects of HIV symptoms, including

ART side effects, and that these symptoms would contribute to decreased treatment adherence (Beusterien et al., 2008). This prediction was primarily based on the results of recent work, among mostly non-cannabis using HIV populations, showing generally poor adherence to HIV treatment (Chesney 2003; Solomon and Halkitis 2008). On the other end of the continuum, we expected similarly low HIV treatment adherence and a heightened experience of HIV symptoms/ART side effects among individuals who were cannabis dependent. This prediction was based on prior literature indicating an association between heavy cannabis use and suboptimal treatment adherence (Wilson et al., 2004), as well as the literature pointing to the detrimental psychological and health-related effects of dependent cannabis use (Zvolensky et al., 2010). Finally, based on prior work showing that cannabis use for specific symptom alleviation (e.g., nausea) is beneficial in terms of adherence (de Jong et al., 2005), we hypothesized that non-dependent cannabis users may actually exhibit greater ART adherence and fewer and less severe HIV symptoms/ART side effects than the other two groups.

So as to provide a rigorous test of the association between cannabis use status and antiretroviral medication adherence, a multi-method approach was employed, with both objective (i.e., pill count, blood test) and subjective (i.e., self-report) measures of adherence. Additionally, both alcohol and tobacco use were assessed and considered as covariates as they have been shown to be associated with both cannabis use (James et al., 1994; Kandel et al., 1997) and ART adherence (Kalichman et al., 2012; Bonolo et al., 2008; Shuter & Bernstein, 2008).

Method

Participants

Participants were 180 HIV positive individuals (39 female; $M_{age} = 48.21$ years, SD = 8.61). In terms of ethnicity, 38.9 % of participants identified as Black/Non-Hispanic, 28.9 % as White/Caucasian, 13.9 % as Black/Hispanic, 11.1 % as Hispanic, 1.1 % as Asian, and 6.1 % as "Other." For inclusion in the study, participants had to be (1) HIV positive; (2) currently prescribed at least one antiretroviral medication, and (3) undergoing treatment at an outpatient HIV treatment clinic. In addition, one-third of the sample ($n = 60$) met DSM-IV criteria for current cannabis dependence[1] (CD), one-third of the sample ($n = 60$) were non-dependent cannabis users (C; use in the past 30 days), and one-third of the sample ($n = 60$) reported no cannabis use within the past 6 months (NC). See Table 1 for a breakdown of demographics for each group.

Measures

Descriptive characteristics

Demographic characteristics such as age, gender, ethnicity/race, marital status, and years of education were collected during the phone interview and re-confirmed at the in-person interview.

Psychiatric diagnoses

Prevalence of current Axis-I diagnoses, including cannabis dependence (See footnote 1), was determined by the Structured Clinical Interview-Non-Patient Version for DSM-IV (First et al., 1995). The SCID-I–N/P was administered by trained research assistants. In terms of training, before administering the SCID-I–N/P in the context of the study, each trainee was required to (1) view 3–4 videotaped or live SCID-I–N/P administrations by senior interviewers at the National Center for PTSD, with the comparison of the trainees ratings to those of the senior interviewer, and (2) administer 6–10 SCID-I–N/P interviews in the presence of a senior interviewer with the requirement that trainees diagnoses match those of the senior interviewer on at least 4 of 5 consecutive administrations. Additionally, all interviews were audio-recorded and diagnoses were confirmed by the first author, a clinical psychologist, following a review of recorded interviews.

Viral load and CD4 cell count

Participant viral load (copies/mL) and absolute CD4 lymphocyte count (cells/uL) was obtained from each participant's most recent blood test at his/her HIV clinic, via medical record review, whether that was prior to or following the study assessment session. The average number of days between the study assessment and the viral load blood test was 22.33 (SD = 80.50), while the average number of days between the study assessment and the CD4 cell count obtained via blood test was 22.81 (SD = 83.74). Viral load and absolute CD4 cell count were used in the present study as a reflection of the participant's HIV status, burden of infection, and response to ART (Mellors et al., 1997; U.S. Health Resources and Services Administration, 2012). For the present study, consistent with prior work (Mellors et al., 1997), viral load was log transformed and absolute CD4 count was standardized (cells/uL).

[1] Diagnostic criteria for cannabis dependence were consistent with the definition set forth in the DSM-IV-TR (APA, 2000), with the addition of withdrawal, as proposed for DSM-5 (Budney et al., 2004).

Table 1 Demographics, co-occurring diagnoses, and substance use among individuals with cannabis dependence (CD), non-dependent cannabis use (C), and no recent history of cannabis use (NC)

Variable	CD ($n = 60$)[a]	C ($n = 60$)[a]	NC ($n = 60$)[a]	Group comparisons
Age (*M* [*SD*])	46.32 (8.02)	47.37 (8.78)	50.92 (8.49)	$F(2,172) = 4.80$**
Male (*n* [%])	48 (80.00)	49 (81.70)	44 (73.30)	$\chi^2 = 1.38$
Race/ethnicity				$\chi^2 = 11.67$
African American/ Non-hispanic (*n* [%])	27 (45.00)	21 (35.00)	22 (36.70)	
Caucasian (*n* [%])	18 (30.00)	15 (25.00)	19 (31.70)	
Hispanic (*n* [%])	3 (5.00)	7 (11.70)	10 (16.70)	
African American/ Hispanic (*n* [%])	10 (16.70)	9 (15.00)	6 (10.00)	
Asian (*n* [%])	− (−)	1 (1.70)	1 (1.70)	
Other (*n* [%])	2 (3.30)	7 (11.70)	2 (3.30)	
Education (*M* [*SD*])	3.70 (1.23)[b]	4.17 (1.56)[b]	4.38 (1.78)[b]	$F(2,173) = 3.05$*
Total # of medications (*M* [*SD*])	2.57 (1.01)	2.27 (1.05)	2.38 (1.09)	$F(2,176) = 1.20$
Number of years HIV-infected	13.94 (7.53)	13.78 (8.12)	15.45 (8.25)	$F(2,168) = 0.75$
Co-occurring diagnoses				
Abuse/dependence of illicit substance other than cannabis (*n* [%])	49 (81.70)	46 (76.70)	39 (65.00)	$\chi^2 = 4.61$
Mood disorder (*n* [%])	16 (26.70)	8 (13.30)	11 (18.30)	$\chi^2 = 3.48$
Anxiety disorder (*n* [%])	31 (51.70)	22 (36.70)	25 (41.70)	$\chi^2 = 2.85$
Cannabis use (*M* [*SD*])	7.03 (1.81)[c]	5.56 (2.38)[c]	–	
Alcohol use (*M* [*SD*])	4.00 (5.39)	2.38 (2.93)	1.03 (1.80)	$F(2,177) = 9.71$**
Tobacco use (*M* [*SD*])	7.58 (13.44)	6.06 (7.63)	4.00 (6.66)	$F(2,177) = 2.06$

[a] The number of participants in each group for each analysis varies slightly due to the exclusion of extreme outliers or missing data

[b] Value corresponds to a level of education between high school graduate (=score of 3), college partially completed (=score of 4) and graduation from a 2-year college (=score of 5)

[c] A score of 5–6 = use of cannabis slightly more than once per week, but less than daily, while a score of 7–8 = use of cannabis daily to more than once a day. Cannabis use = frequency of past 30 day use as indexed by the MSHQ. Alcohol use = total volume (frequency × quantity) of alcohol consumed (as measured by questions 1 and 2 of the AUDIT). Tobacco use = cigarettes/day. No differences were examined between groups in terms of cannabis use frequency due to the nature of these groups being inherently different in terms of frequency of use, with one group not using at all

* $p < 0.05$

** $p < 0.01$

Objective measure of antiretroviral medication adherence

A Pill Count Tracking Form (PCTF) was used to calculate the percentage of prescribed doses that participants took since their last medication refill. The PCTF, similar to pill tracking forms used in prior research, is used to track the number of each patient's ART medications, the number of pills that each patient should have remaining (based on pharmacy records or the last count), and the number of extra pills that the patient has (Osterberg & Blaschke, 2005). Similar to previous research, the pill count derived adherence rate was calculated as the number of doses taken divided by the number expected to be taken as prescribed to yield a total percentage of each patient's adherence to all ART medication(s) (Paterson et al., 2000). Additionally, number of ART medications were counted during the pill count and duration of HIV infection was assessed via self-report.

Self-report measure of antiretroviral medication adherence

The Adherence Questionnaire (AQ) is a 28-item measure that assesses prescribed ART medication doses, the frequency of taking medications at the correct times and in the correct manner, rated on a 7 point Likert-type scale (0 = *"never"* to 6 = *"all the time"*), and the reasons for missed doses (Osterberg & Blaschke, 2005). The AQ is derived from the AIDS Clinical Trials Group's self-report

medication adherence measure and has shown good psychometric properties (Chesney et al., 2000). Some studies suggest that shorter recall periods result in more accurate self-reports (Wagner & Miller, 2004; Simoni et al., 2006). Yet, as ART dosing has become more simplified, sufficient variability in adherence over a several day recall period (i.e., 3–4 days) is severely limited (Paterson et al., 2000; Simoni et al., 2006). In this case, longer recall periods may yield more valuable data. Furthermore, a recall period of at least 7 days insures that a weekend, which is often associated with adherence difficulties, will be included (Simoni et al., 2006). Accordingly, two different recall periods were used for self-reported adherence (Kleeberger et al., 2001; Murphy et al., 2004). The total number of missed doses in the past 4 days and past 2 weeks, in conjunction with the total number of possible doses during the past 4 days and past 2 weeks, were used to yield both 4-day and 2-week percent self-reported adherence scores.

HIV symptoms and ART side effects

The Health Status Questionnaire (HSQ) is a 43-item measure that was developed by the AIDS Clinical Trials Group to assess health status and outcomes for HIV and AIDS patients, and has shown good psychometric properties (Chesney et al., 2000). The HSQ assesses general health, energy, as well as social, physical, and cognitive functioning. The HSQ also assesses 20 common HIV symptoms/ART side effects on a five point Likert-type scale (0 = *"I do not have this symptom"* to 4 = *"I have this symptom and it bothers me a lot"*). Within the present study, similar to prior work (Ammassari et al., 2001), we did not differentiate between HIV symptoms and ART side effects due to their significant overlap. In the current study, a total score was used to index the frequency/severity of self-reported HIV symptoms/ART side effects, with lower scores suggesting a relative absence of symptoms/side effects.

Cannabis use

The Marijuana Smoking History Questionnaire (MSHQ; Bonn-Miller & Zvolensky, 2009) is a 21-item measure that assess the frequency, patterns, and history of cannabis use. In the present study, the MSHQ was used to index frequency of cannabis use. Specifically, participants indicated on a 9-point Likert-type scale ("0" = *No use* to "8" = *More than once a day*) their use of cannabis during the 30 days prior to assessment. The MSHQ has been used extensively in prior work to assess frequency of cannabis use (Bonn-Miller et al., 2007).

Alcohol use

The Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1992) is a 10-item screening measure developed by the World Health Organization to identify individuals with alcohol problems. Most items are rated on a 5-point Likert scale from (0) *never* to (4) *daily* or *almost daily*. There is a large body of literature attesting to the psychometric properties of the AUDIT (Saunders et al., 1993). In the present investigation, the frequency and quantity items of the AUDIT were used to index alcohol consumption.

Tobacco use

The Smoking History Questionnaire (SHQ; Brown et al., 2002) is a self-report questionnaire used to assess smoking history and pattern. The SHQ includes items pertaining to smoking rate, age of onset of smoking initiation, and years of being a daily smoker, and number of serious quit attempts made. The SHQ has been successfully used in previous studies as a measure of smoking history (e.g., onset of regular smoking) and pattern (e.g., number of cigarettes smoked per day; Brown et al., 2002; Zvolensky et al., 2004). In the present study, the SHQ was used to index rate of tobacco use (i.e., average number of cigarettes smoked per day).

Procedure

Interested persons, responding to flyers posted throughout a VA Medical Center as well as in a number of community outpatient HIV clinics in the San Francisco Bay area, contacted the research team and were provided with a detailed description of the study via phone. Participants were then initially screened for eligibility and, if eligible, scheduled for an appointment. Participants were instructed to bring all of their medications to the study appointment. Upon arrival to the laboratory, each participant provided written consent to participate in the research study. Next, participants were administered the SCID I–N/P (First, et al., 1995) by trained interviewers to assess key exclusionary and inclusionary criteria. If deemed eligible, participants then completed a battery of self-report measures and participated in a pill count. At the conclusion of this appointment, participants were compensated $50 for their efforts. Following the appointment, medical records for each participant were accessed to obtain most recent viral load and absolute CD4 information. All study procedures were approved by the Stanford University Institutional Review Board (IRB) and Mills Peninsula IRB.

Data analytic plan

First, cannabis groups (i.e., CD, C, and NC) were compared in terms of demographics variables, other substance use, psychopathology, and HIV-related factors to determine potential covariates for each analysis. In terms of the primary analyses, in the first set of analyses we examined the relation between cannabis group (CD, C, and NC) and the 4 indices of HIV antiretroviral treatment adherence (i.e., pill count, self-report, log viral load, and absolute CD4 count) in 4 separate Analyses of Variance (ANOVA). For those ANOVAs that were significant, relevant covariates were included in Analyses of Covariance (ANCOVA) to determine if effects remained. A second set of analyses was then conducted to determine the relation between cannabis group (CD, C, and NC) and HIV symptoms/medication side effects. Similar to the first set, an ANOVA was first conducted and then an ANCOVA was used to determine whether the effect remained after including covariates. For all ANOVA procedures that did not meet the criterion of homogeneity of variances, a Welch correction was used. For each significant ANOVA, a Tukey HSD or Dunnett T3 post hoc test, depending on whether there was homogeneity of variances, was run to determine group differences.

Results

Descriptive and preliminary analyses

As presented in Table 1, the groups significantly differed in terms of age, highest level of education, and alcohol consumption. More specifically, a Tukey HSD post hoc test revealed that (1) dependent cannabis users (CD) were significantly younger than those with no recent history of use (NC); (2) dependent cannabis users (CD) had a significantly lower level of completed education than those with no recent history of use (NC); and (3) dependent cannabis users (CD) consumed significantly more alcohol than either non-dependent cannabis users (C) or those with no recent history of cannabis use (NC). Accordingly, age, education, and alcohol use served as covariates in primary group comparisons.

Cannabis and ART Adherence

A significant effect of group on pill count was observed [Welch(2,87.15) = 6.37, $p = 0.003$], such that those in the CD group had significantly lower adherence than those in the C group. A significant effect for group on self-reported adherence over past 4 days was also observed [Welch(2,106.00) = 3.26, $p = 0.042$], though post hoc tests were not able to discern the nature of the group differences. However, no significant effects were observed for group with self-reported adherence over past 2 weeks [F(2,169 = 0.76, $p = 0.47$]. A significant effect of group on log viral load was also observed [Welch(2,101.39) = 3.23, $p = 0.044$], such that those in the CD group had significantly higher log viral load than those in the NC group. No significant effects were observed for group in terms of CD4 count [F(2,177) = 0.72, $p = 0.487$]. See Table 2 for a summary of results.

After accounting for the effects of age, education, and alcohol consumption, an ANCOVA revealed that the association between group and pill count to remain statistically significant [F(2,124) = 3.93, $p = 0.022$]. However, after accounting for the effects of age, education, and alcohol consumption, ANCOVAs revealed the association between cannabis group and self-reported adherence [F(2,156) = 2.52, $p = 0.084$] and log viral load [F(2,165) = 1.37, $p = 0.256$] to no longer be statistically significant, though the effect for self-reported adherence remained at a trend.[2]

Cannabis and HIV symptoms/ART side effects

In terms of the relation between group and HIV symptoms/medication side effects, the ANOVA revealed a significant effect [F(2,171) = 5.23, $p = 0.006$], such that those in the CD group reported significantly more frequent and severe HIV symptoms/medication side effects than those in either the C or NC groups (see Table 2). After accounting for the effects of age, education, and alcohol consumption, the ANCOVA revealed the association to remain statistically significant [F(2,157) = 3.06, $p = 0.050$].[3]

Subsidiary analysis

To further probe the effect observed for group in terms of viral load, a Chi-square test was conducted to determine cannabis group differences in terms of the detectability of viral load. Specifically, viral load values were categorized as either detectable or non-detectable based on a cut-off of 20–48 copies/mL. This method of dichotomizing viral load values has been used in prior work (Gandhi and Deeks, 2012). Similar to the results observed in the ANOVA, those in the CD group were significantly more likely to have a

[2] Thirteen participants were excluded from analyses involving pill count adherence due to inability to calculate pill counts.

[3] As absolute CD4 count and viral load have been associated with disease progression (Mellors et al., 1997; Viana et al., 2011), analyses were repeated with both absolute CD4 count and log viral load serving as additional covariates in the ANCOVA model. With these additional covariates, the significant effect for group in terms of HIV symptoms/medication side effects, remained [F(2,155) = 3.26, $p = 0.041$].

Table 2 ANOVA group differences in adherence and HIV symptoms/medication side effects between individuals with cannabis dependence (CD), non-dependent cannabis use (C), and no recent history of cannabis use (NC)

Variable	CD Mean (SD)	C Mean (SD)	NC Mean (SD)	$F(df)$	p	η_p^2
Pill count adherence	0.74 (29)	0.90 (21)	0.77 (29)	6.37 (2,87.15)^	0.00	0.07
Self-reported adherence						
Past 4 days	0.93 (0.15)	0.93 (0.15)	0.97 (0.09)	3.26 (2,106.00)^	0.04	0.03
Past 2 weeks	0.93 (0.15)	0.96 (0.10)	0.96 (0.14)	0.76 (2,169)	0.47	0.01
Viral load	2.00 (0.85)	1.84 (0.83)	1.71 (0.37)	3.23 (2,101.39)^	0.04	0.03
CD4	501.02 (302.58)	556.23 (268.46)	554.70 (287.86)	0.72 (2,177)	0.49	0.01
HIV symptoms/side effects	37.62 (18.16)	27.47 (19.32)	29.12 (15.90)	5.23 (2,171)	0.01	0.06

^ = Welch corrected ANOVA due to significant Levene's test (indicating inequality of variances). Adherence values are indicative of percent adherence (e.g., 0.90 = 90 %)

detectable viral load than those in either the C or NC groups [χ^2 (2, $N = 180$) = 22.05, $p = 0.000$].

Discussion

The present study aimed to determine the association between cannabis use status (i.e., CD, C, NC) and antiretroviral medication adherence, as well as HIV symptoms/ART side effects, among a sample of HIV-positive individuals. Partially consistent with hypothesis, those in the CD group generally reported lower adherence and greater HIV symptoms/ART side effects than the other two groups (i.e., C, NC).

In terms of pill count, those in the CD group reported significantly lower adherence than those in the C group, and the CD group tended to report lower self-reported adherence (4-day) than those in the NC group. With regard to viral load, again, those in the CD group had higher viral load than those in the NC group, while those in the CD group reported more frequent and severe HIV symptoms/ART side effects than those in either of the other two groups. These findings are consistent with prior work that has shown heavy cannabis use to be associated with non-adherence (Wilson et al., 2004) as well as work showing cannabis dependence to be related to a variety of negative psychological and health-related factors (Zvolensky et al., 2010). Here, it is also noteworthy that the observed findings for pill count and HIV symptoms/ART side effects remained after accounting for the effects of age, highest level of education, and alcohol consumption, which were shown to differ between cannabis groups.

Though it was hypothesized that both the CD and NC groups would report lower adherence and more frequent and severe HIV symptoms/ART side effects than the C group, there were in fact no differences observed between NC and C groups in any of the analyses; differences were only observed between the CD group and either or both of the other two groups, depending on the outcome. This lack of differences between C and NC groups was not expected given that those in the NC group do not use a coping mechanism (i.e., cannabis) that has been shown to reduce HIV symptoms and ART side effects (Prentiss et al., 2004; Abrams et al., 2007; Furler et al., 2004; Haney et al., 2007) and thus improve adherence (de Jong et al., 2005). Indeed, our findings suggest that moderate cannabis use (e.g., use more than once per week but less than daily), as compared with non-use, may not be meaningfully associated with symptom relief or medication adherence. Further examination of these group differences is needed to ascertain the functions of cannabis use among individuals with HIV who use cannabis moderately (e.g., to alleviate HIV medication induced-nausea, to alleviate negative affect, facilitate sleep, or for recreation).

It is also noteworthy that viral load, but not absolute CD4 count, was shown to differ between groups. Observing viral load changes in the absence of CD4 count changes is not unusual (Ironson, 2005). It is possible that no effect was observed for absolute CD4 count because viral load may be a more reliable marker of responsiveness to ART as CD4 count changes are sometimes delayed in relation to changes in viral load and, for some patients, do not stably increase even with durable undetectable viral load (U.S. Health Resources and Services Administration [USHRSA], 2012; U.S. Department of Health and Human Services [USDHHS], 2012). Additionally, in terms of self-reported ART adherence, it is noteworthy that group differences were observed for 4-day, but not 2-week, self-reported adherence. Though it is possible that 4-day data are more accurate (Wagner & Miller, 2004; Simoni et al., 2006), future work would benefit from further examining concordance or discordance between different windows of self-reported ART adherence among HIV+ individuals with varying degrees of cannabis use.

There are many potential clinical implications from the present findings, however, it is important to note that the

cross-sectional nature of the study does not allow for the interpretation of directionality of findings and thus clinical implications must be interpreted with some caution. Indeed, it is just as likely that cannabis dependence led to poor adherence as it is that poor adherence was associated with more severe HIV symptoms which led individuals to use cannabis for coping-oriented reasons, leading to dependence. In either case, cannabis dependence appears to be an indicator of increased risk of poor adherence and more severe HIV symptoms/ART side effects.

Findings suggest a need to thoroughly and accurately assess and address cannabis use among HIV positive individuals who are prescribed antiretroviral medication. Indeed, it may not be enough to assess whether an individual simply uses cannabis, but also the frequency and duration of use, as well as problems associated with use, tolerance, and withdrawal, so as to be able to accurately determine dependence. Second, and related, findings suggest the potential need for specific interventions for HIV positive individuals with cannabis dependence. Cannabis dependent individuals in the present study had between 74 % (pill count) and 93 % (self-report) adherence, and evidence of poorer viral suppression. Though pill count data revealed higher adherence for non-dependent cannabis users, both pill count and self-report data on adherence was also lower than 95 %, on average, for this group as well. Existing brief interventions that can be used in primary care and specialty care settings (e.g., Stephens et al., 2007) may be useful in terms of reducing problematic cannabis use and increasing antiretroviral adherence among these individuals. Finally, as some data suggest that even low levels of cannabis use are associated with psychological problems (Zvolensky et al., 2008), the lack of differences between cannabis non-users and non-dependent users provide some initial doubt as to the clinical utility of recommending cannabis for those with HIV.

Though the present study provides a more detailed picture of the relations between cannabis use and antiretroviral adherence and HIV symptoms/ART side effects, it is not without limitation. First, the present study was cross-sectional and thus unable to determine the prospective association between varying degrees of cannabis use and adherence or symptoms. Indeed, it remains unclear whether cannabis dependence led to poor adherence and symptoms or whether more severe HIV symptoms resulting from poor adherence led to cannabis dependence via coping-oriented use. Related, though the employed measurement design was a study strength, we were not able to discern pill count or self-reported adherence as well as would have been possible with multiple assessments to establish a stable baseline level of adherence (e.g., ecological momentary assessment). Future studies would benefit from examining the studied associations longitudinally, and conducting blood draws (for viral load/cd4 count and THC level) at the same time as the other assessments. Such improvements in design and measurement would also warrant more advanced methods of statistical analysis (e.g., structural equation modeling), where multiple observed variables could serve as indicators of an overarching latent "adherence" variable. Though the present study was quite ethnically diverse, almost 80 % of the sample was male. Though the present study had a higher percentage of females with HIV than is represented in the San Francisco bay area (Das et al., 2010), future work would benefit from recruiting a more gender-diverse sample from different geographic areas. Finally, though cannabis dependence was assessed using the most current and rigorous criteria, the collection of additional contextual information related to cannabis use (e.g., timing of cannabis ingestion relative to dosing schedule) may help improve our understanding of the differences observed in the present study. Related, the collection of additional information on factors such as substance use motivation, emotion regulation, and cognitive functioning, in future prospective studies, would allow for the determination of malleable mechanisms that may underlie the observed relations, providing a more nuanced understanding of the association between cannabis use and antiretroviral medication adherence and HIV symptoms/ART side effects.

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