



The Association Between Marijuana Use and HIV Continuum of Care Outcomes: a Systematic Review

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Abstract

Purpose of Review Approximately 77% of HIV-infected adults report lifetime marijuana use. Given the high rates and social acceptability of marijuana use among HIV-infected individuals, it is important to gain a stronger understanding of if, and how, marijuana impacts HIV care cascade outcomes. The purpose of this study is to systematically review recent articles that assess the relationship between marijuana use and HIV continuum of care outcomes.

Recent Findings One hundred and ninety articles from PubMed were considered for inclusion, and 15 were included in the review. The studies focus on marijuana use among HIV-infected individuals aware of their serostatus ($k = 4$), individuals engaged in treatment ($k = 1$), marijuana use in association with adherence to antiretroviral medications ($k = 6$), and marijuana use in relation to multiple stages of the HIV care cascade ($k = 4$). Preliminary findings from the small number of studies revealed an association between marijuana use, especially current heavy use, and HIV seropositivity. However, results from studies assessing marijuana use and treatment engagement and adherence to antiretroviral medications were inconsistent and inconclusive.

Summary Additional research is needed to assess the nuanced relationship between marijuana use and HIV continuum of care outcomes, especially among subgroups of HIV-infected individuals, such as men who have sex with men and young adults.

Keywords Marijuana · HIV/AIDS · Continuum of care

Introduction

In 2016, over 36 million people globally were living with HIV [1]. In the USA, over 37,000 people became newly infected with HIV in 2014 [2] with approximately 1.2 million Americans living with HIV [2]. Despite the significant decline (18%) in new incident infections from 2008 to 2014, HIV remains a public health concern and was directly attributed to 6721 deaths in

2014 [2]. Further exacerbating this issue is illicit drug use, which increases the risk for contracting HIV [3, 4], and is also associated with other health, legal, and social consequences among individuals living with HIV [5, 6]. Rates of illicit drug use are high among this population, with 16.6% reporting lifetime injection drug use and 64.4% reporting lifetime non-intravenous use of illicit drugs [7]. A large body of literature is available on illicit drug use, especially injected drugs, such as cocaine, heroin, and methamphetamine, among individuals living with HIV [4], but a much smaller number of studies have focused on marijuana use. Given the changing sociopolitical landscape of marijuana in the USA, and increasing medicalization and legalization, it is important to gain a stronger understanding of if, and how, marijuana use impacts HIV-related treatment outcomes among individuals living with HIV.

The rates of marijuana use among HIV-infected populations are high. In a nationally representative sample of HIV-infected and uninfected adults, approximately 77% of HIV-infected adults reported lifetime marijuana use compared to 44.5% of their uninfected counterparts [8•]. Similar patterns were found with reports of past year (34.2% versus 11.1%) and past month (24.9% versus 6.7%) marijuana use among HIV-infected and uninfected adults [8•]. Among a sample of young HIV-infected

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Black men who have sex with men (MSM), approximately 50% of participants reported daily or weekly marijuana use [9]. Although rates of marijuana use are typically highest among young adults, approximately 42% of HIV-infected adults over the age of 50 reported current marijuana use, with an average of 7.2 days of use in the past month [10]. High rates of marijuana use are also found among HIV-infected adults who are engaged in HIV care, with 31% of HIV care enrollees meeting criteria for marijuana abuse or dependence [11•].

While some data suggest that marijuana may stimulate appetite, improve weight gain, and address symptoms of AIDS-related wasting syndrome [12] and HIV-associated neuropathic pain [13], collectively, data are inconclusive for the potential therapeutic benefit of marijuana for HIV-infected individuals [14, 15]. Further, marijuana use may be associated with neurocognitive impairment among HIV-infected individuals [16]. A recent review synthesized literature examining the effects of marijuana on memory functioning among HIV-infected individuals [17•]. In their review, Skalski and colleagues [17•] hypothesized that marijuana use among HIV-infected individuals may result in more pronounced memory impairment but noted the need to further study the neurocognitive effects of marijuana use among individuals living with HIV. With the increasing popularity and social acceptability of marijuana, it is also important to understand the link between marijuana use and outcomes along the HIV care cascade.

Consistent with the U.S. National HIV/AIDS Strategy, the HIV care cascade refers to the continuum from HIV testing and diagnosis to be aware of one's serostatus through sustained viral suppression [18]. The care cascade conceptualizes key "steps" along the care continuum to include testing/diagnosis, linkage to HIV care, receipt of HIV care, retention in HIV care, adherence to antiretroviral (ARV) medications, and viral suppression [2, 18]. The U.S. National HIV guidelines are to ensure that 90% of all individuals are tested, 90% receive HIV care, and 90% are virologically suppressed via ARV medications [19, 20]. One US study estimated that only 79% of HIV-infected individuals are aware of their serostatus, with 59% linked to care, 40% retained in care, 24% prescribed ARVs, and 19% virally suppressed [21]. While sustained viral suppression is an efficacious strategy to reduce infectivity, linkage and retention in HIV care are often poor, with lower retention in HIV care among individuals using illicit substances [18]. While some have argued that illicit substance use is associated with poorer HIV care cascade outcomes, there is a paucity of data examining the potential association between marijuana use, specifically, and HIV care cascade outcomes.

The primary aim of this review is to synthesize the literature examining the association between marijuana use and HIV care cascade outcomes. We reviewed studies examining the relation between marijuana use and the HIV care cascade outcomes of the following: (a) HIV testing/diagnosis and being aware of one's serostatus, (b) linkage to HIV care, (c)

retention in HIV care, (d) adherence to antiretroviral (ARV) therapy, and (e) viral suppression. We then discuss gaps in the extant literature and identify potential future directions to advance research examining the association between marijuana use and HIV care cascade outcomes.

Methods

This study is a systematic review of studies assessing the association between marijuana use and HIV continuum of care outcomes. Figure 1 displays the search strategy that identified relevant articles as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were identified by searching through the PubMed database. The search took place on October 6, 2017. Several relevant keywords were used in the search, including (Marijuana OR Cannabis) AND (HIV positive OR HIV infected OR living with HIV OR HIV/AIDS). The search was limited to articles that were published in the last 5 years. The titles and abstracts of articles identified via PubMed were searched to determine if the articles met the following criteria: (1) include marijuana use as an independent or dependent variable in the study, (2) must focus on adolescents or adults who are living with HIV or AIDS, either solely or as a comparison group (e.g., outcomes among HIV-infected individuals relative to HIV uninfected individuals), and (3) conducted among a population residing in the USA. In an effort to further refine and organize the studies identified in the search, an additional inclusion criterion was added: (4) must examine the association between marijuana and HIV continuum of care outcomes (e.g., HIV testing/diagnosis and being aware of one's serostatus, linkage to HIV care, retention in HIV care, adherence to ARV therapy or viral suppression). Studies were excluded if they (1) only focused on marijuana or HIV/AIDS risk behaviors (e.g., must focus on actual use among a sample that is living with HIV), (2) combined data from HIV-infected and HIV uninfected individuals in analyses (i.e., no separate analyses for HIV-infected individuals), and (3) were a systematic review/meta-analysis, report or case study.

As shown in Fig. 1, 190 articles were identified through PubMed. Two independent reviewers assessed the titles and abstracts for all 190 articles to determine if they met inclusion criteria. A third reviewer was consulted in cases where the two initial reviewers disagreed over the inclusion of an article. A total of 129 articles were excluded at the first level of review because they did not meet the inclusion criteria (e.g., did not include outcomes among HIV-infected individuals). In an effort to better organize and synthesize findings from the identified studies, the remaining 61 articles were reviewed further to assess for outcomes related to the HIV continuum of care. Ultimately, a total of 15 studies were included in the review.

Flow Diagram for Marijuana and HIV Continuum of Care Outcome Articles

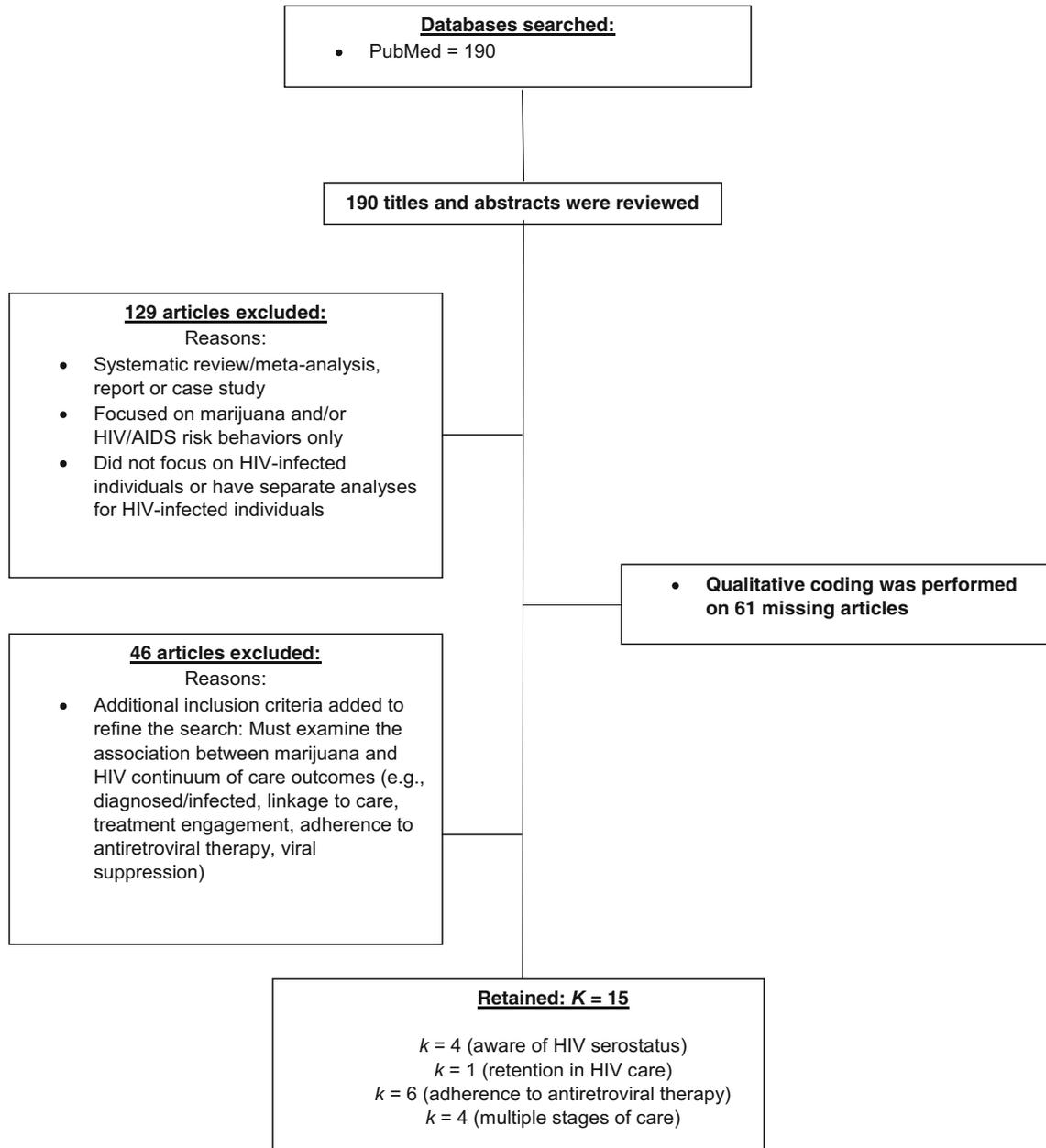


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for marijuana and HIV continuum of care outcome articles

For the purposes of this review, marijuana use was defined as any self-reported and/or biologically verified use over a lifetime (e.g., self-reported past month marijuana use). The review examined the relationship between marijuana use and HIV continuum of care outcomes including (1) among individuals who were tested for HIV and aware of their HIV serostatus, (2) linkage to HIV care, (3) retention in HIV care, (4) adherence to ARV therapy, and (5) viral suppression. As a reference, we utilized Centers for Disease Control and Prevention guidelines for measurement of HIV care continuum outcomes.

Results

Sample Description

This review identified 15 current studies assessing the link between marijuana and HIV continuum of care outcomes (Table 1). The studies focused on marijuana use among individuals who were aware of their HIV serostatus ($k = 4$), as well as the link between marijuana and retention in HIV treatment ($k = 1$), adherence to ARV ($k = 6$), and multiple stages of care ($k = 4$). No studies focused specifically on marijuana use and

Table 1 Marijuana and HIV continuum of care studies, 2012–2017

Author, year	Population characteristics	Marijuana variables	HIV-related variables	Other relevant variables	Major finding(s)
HIV-infected/aware of serostatus adherence					
Esposito-Smythers, Brown, Wolff et al., 2014	17 HIV-positive young adults (ages 18–24 years) at three HIV community clinics participating in a pilot trial for an integrated cognitive behavioral and contingency management intervention for alcohol and/or cannabis use disorders; 6% women; average age of 21.1 (SD = 1.3)	(1) Urine drug screens, (2) marijuana-related problems	(1) Sexual behavior, (2) medication adherence	N/A	(1) A statistically significant trend toward reductions in days of past month marijuana use at post-intervention (small effect) and marijuana related problems across follow-ups (medium to large effect)
Reback & Fletcher, 2014	Street encounters with 5599 substance-using men who have sex with men; 13.4% HIV-infected	(1) Self-reported past month marijuana use	(2) Self-reported HIV status	N/A	(1) Each additional day of marijuana use was associated with HIV-positive status
Adams, Bryant, Edelman et al., 2017	3099 HIV-infected men in the Veterans Aging Cohort Study; median age 49 years; 37.6% heterosexual, 31.9% men who have sex with men, 30.5% not sexually active	(1) Self-reported past year marijuana use	N/A	(1) Mortality risk	(1) Marijuana use was not associated with mortality risk
Keen, Abbate, Blanden et al., 2017	Community sample of 95 HIV-positive heterosexual Black adults; 50.5% women; mean age 45.76 years (11.22)	(1) Urine drug screens	(2) CD4 and CD8 cell count	N/A	(1) Marijuana-positive patients had significantly higher CD4+ and CD8+ counts than their marijuana-negative counterparts
Retention in HIV care					
Kipp, Rebeiro, Shepherd et al., 2017	Retrospective cohort study of 1791 HIV-positive adults at the Vanderbilt Comprehensive Care Clinic; median age 45 years; 26% women	(1) Any self-reported marijuana use, (2) frequency of self-reported marijuana use	(1) Failure to be retained in the following calendar year, (2) missed visits	N/A	(1) Marijuana use was not associated with the Institute of Medicine retention outcome, but was associated with missing the next scheduled appointment, (2) a non-linear dose response was observed for frequency of marijuana use and missed visits, with daily users having the highest risk compared to non-users
Adherence to antiretroviral (ARV) therapy					
Attonto, Devieux, Lerner et al., 2014	246 HIV-infected adults with a history of alcohol abuse or dependence within the past 2 years participating in a prospective randomized controlled trial; mean age 45.24 years (SD = 7.04); 34% women	(1) Timeline follow-back (total number of times used marijuana in the prior 3 months)	(1) ARV adherence, (2) barriers to adherence	N/A	(1) Small positive association between marijuana use and ARV adherence approached significance

Table 1 (continued)

Author, year	Population characteristics	Marijuana variables	HIV-related variables	Other relevant variables	Major finding(s)
Newville, Berg, & Gonzalez et al., 2015	100 HIV-infected individuals receiving methadone maintenance treatment in the Bronx, New York; 53.5% women	(1) Self-reported past month marijuana use	(1) ARV adherence, (2) medication side effects	N/A	(1) Marijuana use was the single substance of abuse most strongly associated with non-adherence to highly active ARV
Gross, Hosek, Richards et al., 2016	387 HIV-positive young African-American males on ART selected from a cross-sectional assessment of youth living with HIV receiving medical care within the Adolescent Trials Network for HIV/AIDS Interventions; mean age 21.3 years (SD = 2.1)	(1) Use and frequency (the past 3 months) of marijuana	(1) ARV adherence	N/A	(1) Frequency of marijuana use during the past 3 months was found to be strongest independent predictor of adherence, (2) among participants with infrequent cannabis use, 72% reported full adherence compared to only 45% of participants who used marijuana frequently, (3) Participants who engaged in weekly marijuana use were least likely to be adherent
Kuhns, Hotton, Garofalo et al., 2016	212 HIV-positive adolescents enrolled in one of two pilot randomized controlled trials on the efficacy of two separate interventions to improve adherence; mean age 24 years; 11% women; 91% behaviorally infected	(1) Frequency of marijuana use in the past 3 months, (2) marijuana-related problems	(1) ARV adherence, (2) viral load	N/A	(1) Moderate/heavy marijuana use was not significantly correlated with level of adherence
Vidot, Lerner, & Gonzalez, 2017	Community sample of 107 HIV-positive adults; mean age 37 years (SD = 10.5); 34.6% women	(1) Self-reported frequency of use, (2) urine drug screen	(1) Adherence to HIV medication regimen, (2) medication management skills	N/A	(1) No association between marijuana use (self-reported and biologically-confirmed) and adherence nor medication management
Zhang, Wilson, Adedimeji et al., 2017	1799 HIV-infected women in the Women's Interagency HIV study; 42 (range 36–48)	(1) Self-reported marijuana use in the past 6 months	(1) Adherence to ARVN	N/A	(1) Marijuana use predicted suboptimal adherence
D'souza, Matson, Grady et al., 2012	2776 HIV-infected women in the Women's Interagency HIV study; median age 36 years	(1) Self-reported use of marijuana since last visit, (2) self-reported days of marijuana use since last visit, (3) reasons for marijuana use, (4) effect of marijuana use on ARV	(1) Marijuana use within the past 3 months	(1) Comorbid conditions (peripheral neuropathy, asthma, depression, diabetes), (2) quality of life, (3) illicit substance use in the past 6 months, (4) number of sexual partners and condom use in the past 6 months	(1) Relaxation, appetite improvement, reduction of HIV-related symptoms, and social use were reported as common reasons for marijuana use, (2) daily marijuana use was associated with higher CD4 cell count, quality of life and older age, (3) 98% reported that their marijuana use did not impact adherence to ARV medication

Table 1 (continued)

Author, year	Population characteristics	Marijuana variables	HIV-related variables	Other relevant variables	Major finding(s)
Hightow-Weidman, LeGrand, Choi et al., 2017	193 young Black men who have sex with men participating in a randomized controlled trial of an online intervention, HealthMpowerment; mean age 24.91 years (SD = 3.11)	(1) Marijuana use within the past 3 months	(1) Engagement in care, (2) missed visits, (3) ARV uptake, (4) ARV adherence, (5) viral suppression	N/A	(1) Among those in care, individuals with no marijuana use in the prior 3 months were less likely to miss visits, (2) no association between marijuana use and other continuum of care variables
Morgan, Khanna, Skaathun et al., 2016	Longitudinal population-based cohort study among 618 young Black men who have sex with men within South Chicago and adjacent south suburbs; mean age 22.8 years (range 16–29)	(1) Self-reported frequency of marijuana use in the past 12 months (never, intermittent and heavy users)	(1) HIV infected status, (2) linkage to care, (3) retention in care, (4) adherence to ARV, (5) viral suppression	N/A	(1) Heavy marijuana users were more likely to be unaware of their HIV seropositive status, (2) all other stages in the care continuum demonstrated no significant differences between those who use marijuana intermittently or heavily or as a sex-drug and non-users
Okafor, Zhou, Burrell et al., 2017, 914	5914 adult men who have sex with men participating in the Multicenter AIDS Cohort Study (MACS); 46% HIV-infected	(1) Current marijuana use, (2) daily marijuana use	(1) CD4+ cell count, (2) HIV viral load, (3) adherence to ARV	N/A	(1) Among men in the early cohort (recruited before 2001), a HIV+ serostatus compared to a HIV-serostatus was significantly associated a higher prevalence of current and daily marijuana use [no significant association found in the late cohort], (2) statistically significant association between CD4+ cell count and detectable HIV viral load and prevalence of marijuana use

linkage to care or viral suppression, although these areas were assessed in two of the studies that focused on multiple stages of care.

Marijuana Use Among Individuals Aware of Their HIV Serostatus

A pilot study by Esposito-Smythers and colleagues [22] tested the effects of an integrated cognitive behavioral therapy and contingency management (CBT/CM) intervention for young HIV-infected individuals with either an alcohol or cannabis use disorder. There were a total of 14 participants who were mostly other or mixed race (47%), followed by Black (41%), male (94%) with a mean age of 21 years. Substance use outcomes were assessed using the Customary Drinking and Drug Use Record [CDDR; 23] and urine analysis. No statistically significant changes were found for any of the marijuana use outcomes from baseline to follow-up, though trends were in the expected direction for reduction in number of days used, marijuana-related problems, and marijuana withdrawal symptoms. The rate of positive urine drug screens remained the same throughout the study. In addition, these researchers found that one motivator for use among marijuana users with and without a prescription for marijuana were to reduce the side effects of ARV therapy and physical pain; thus, their goal may not have been to achieve abstinence from marijuana but to reduce their use to a level that did not result in impairment. With this in mind, Esposito-Smythers and colleagues [22] concluded that the current pilot study provides preliminary support for the acceptability and feasibility of an integrated CBT/CM intervention for reducing substance use problems among HIV-infected individuals.

Reback and Fletcher [24] investigated the HIV prevalence rate of substance using MSM. Participants were 5599 MSM recruited through HIV prevention outreach encounters in high-risk settings in a large, urban city. The sample was mostly White (47%), followed by Latino (32%), under 39 years old, and primarily identified as gay (84%). Each participant self-reported their HIV status and their substance use in the past 30 days. Overall, Reback and Fletcher [24] found the prevalence rate of HIV among substance using MSM decreased from 20% in 2008 to 8% in 2011. HIV-infected MSM reported significantly more mean days of marijuana use (6.8 [10.2]) compared to MSM who were not HIV-infected (5.2 [9.2], $p < .001$). Controlling for demographic factors, each additional day of marijuana use was associated with increased risk of HIV-positive status among MSM in Los Angeles County (RRR 1.01 [1.01, 1.02]). The authors concluded that while the rate of HIV is decreasing among MSM, marijuana use continues to be a predictor of HIV-positive status [24].

The goal of a study by Adams and colleagues [25] was to assess the impact of marijuana use on the Veterans Aging

Cohort Study (VACS) Index, which is a prognostic indicator of mortality that has been validated. Data were based on 3099 HIV-infected, male veterans drawn from VACS. The veterans were recruited between 2002 and 2010 from eight US Veteran Administration facilities. Participants were mostly non-White (80%) with a median age of 49 years. Each participant completed questionnaires on their substance use and other variables annually over seven waves. At baseline, 15% of the sample reported marijuana use less than once a month to everyday. Adjusted longitudinal analyses indicated marijuana use did not have a negative effect on mortality risk ($\beta = -0.97$, $p = .048$). Given that sociodemographic factors were associated with greater mortality risk than substance use, these researchers concluded that programs aimed at reducing the impact of poverty and racial disparities would be essential for improving the health of male, HIV-infected veterans [25].

To determine how marijuana impacts the immune system among Black HIV-infected individuals, Keen and colleagues [26] investigated differences in lymphocyte count as assessed by cluster differentiation 4 and 8 (CD4+ and CD8+). CD4+ and CD8+ counts were examined in HIV-infected individuals who tested positive for tetrahydrocannabinol (THC) through urine drug screens versus those who tested negative. Participants consisted of 95 Black, heterosexual adults with a mean age of 46 years recruited through the University of Florida Center of HIV/AIDS Research and Education Service Rainbow Center in Jacksonville, FL. Analysis of covariance indicated both CD4+ (621[338]) and CD8+ mean levels (904[461]) were significantly higher among THC+ participants compared to THC- participants (524[360]; 762[338], respectively). In addition, years living with HIV and detectable viral load significantly predicted CD4+ counts above and beyond other variables. Despite differences in CD4+ and CD8+ counts, findings from the study suggest that most of the sample was in good health related to their HIV progression, and the authors concluded that THC does not negatively impact immune function [26].

Marijuana Use and HIV Treatment Engagement

One study investigated the impact of marijuana use on retention in HIV treatment engagement [27]. Participants consisted of 1549 HIV-infected individuals who were mostly White (51%) and male (75%), with a median age of 45 years. Each participant attended two or more medical provider visits in 2011 at a Comprehensive Care Clinic. A short screening questionnaire was administered at each visit assessing self-reported number of times a participant missed taking ARV medication and the number of days they used substances in the last 7 days. The retention outcomes included (1) not meeting the Institute of Medicine's (IOM) definition of two or more provider visits in less than or equal to 90 days and (2) no-show visits. Seventeen percent of participants reported any

marijuana use during 2011 with the majority reporting using between one and six times per week. Those reporting marijuana use tended to be younger, Black, and had a history of injection drug use or other drug use. Although there was no association between marijuana use and the IOM outcome, the findings indicated that any marijuana use was associated with a 37% chance of missing their next medical appointment (adjusted RR 1.37 [1.12, 1.69]) with the highest risk among those reporting marijuana use between seven-14 times per week (1.67 [1.30, 2.15]). Kipp and colleagues [27] concluded that daily marijuana use negatively impacts subsequent HIV medical appointment attendance.

Marijuana Use and Adherence to Antiretroviral Therapy

Attonito and colleagues [28] found a positive relationship between marijuana use and ARV adherence trending toward significance ($\beta = 0.15$, $p = 0.057$) and no significant relationship between marijuana use and viral load among HIV-infected adults with a history of alcohol use disorder. In structural equation modeling, the following regression paths including marijuana were significant: barriers to ARV adherence (e.g., I forgot to take my pills, I am too busy) \times marijuana use was associated with ART adherence ($p < 0.05$; regression coefficient 0.07), but not viral load and support \times marijuana use was associated with viral load ($p < 0.05$; regression coefficient 0.003), but not ART adherence. Barriers to ART adherence was the only independent variable that was significantly associated with ART adherence ($\beta = -9.47$; $p < 0.001$) and viral load ($\beta = 0.30$; $p = 0.002$) in the model.

In a population of methadone-maintained HIV-infected adults living in an urban city, Newville and colleagues [29] found an association between marijuana use and ARV non-adherence, which remained significant after controlling for depression ($p = 0.003$). This relationship has also been further explored among HIV-infected Black adolescents and young adults, where a high level of psychological distress and marijuana use weekly or more frequently for at least 3 months were predictive of ART non-adherence [69% accuracy; 30]. Further, 24% more of these high distress, frequent marijuana using youth were ARV non-adherent when comparing levels of reported self-efficacy to attend appointments, with high-self efficacy being protective. Further, moderate effect predictors in the relationship between marijuana use and adherence included monthly or more frequent use ($p < 0.001$; prediction 54.9% adherent) and marijuana use once or twice ($p < 0.000$; prediction-72.4% adherent; 30).

Another study of primarily behaviorally infected, majority Black youth found no association between moderate/heavy marijuana use and adherence [31]. Further, neither 9-carboxy-THC in urine nor past 30-day, past year, and lifetime marijuana use was associated with medication management

[32]. In a large study of HIV-infected women, general substance use was associated with 61% higher prevalence of suboptimal (0.95%) adherence, after adjusting for calendar year, age, race, employment, depressive symptoms, CD4+ cell count, detectable HIV viral load, and enrollment cohort (aPR = 1.61, 95% CI 1.24–2.09); however, marijuana use alone was not associated with suboptimal adherence after controlling for the aforementioned factors [33]. However, as compared to other substance users, women who used marijuana alone had significantly greater suboptimal adherence (aPR = 1.48, 95% CI 1.11–1.97). Among those who were on single tablet medication regimens, marijuana-only use was associated with a 48% higher rate of suboptimal adherence as compared to no substance use [33].

Marijuana Use and Multiple Stages of Care

D'Souza and colleagues [12] utilized data from the Women's Interagency HIV Cohort, which is a large, multisite, longitudinal study. Participants consisted of 2776 HIV-infected women who from 1994 to 2010 were interviewed twice per year regarding their drug and alcohol use. At baseline, the majority were Black (56%) with a median age of 36 years. From 2004 to 2008, participants were queried about their reasons for marijuana use and whether their use interfered with their ARV medication treatment. Biological data was collected at each visit including CD4 T cell count and HIV viral load. Medicinal versus recreational marijuana was assessed beginning in 2009. D'Souza and colleagues [12] found the rate of marijuana use decreased from 23 to 14% as the women aged, regardless of whether they were receiving ARV therapy or not. Common reasons for use among participants who were current marijuana users included relaxation (85%), appetite stimulation (58%), socializing (41%), and reduction of HIV symptoms (23%). Among the 257 women assessed between 2009 and 2010, over 98% reported their marijuana use does not impact how they take their HIV medication. There was an association between daily marijuana use and higher CD4 cell count, improved quality of life, and older age. The authors concluded that it is not uncommon for HIV-infected women in the USA to use marijuana for recreational and/or medicinal purposes, marijuana use does not impact adherence to ARV treatment, and marijuana is used to alleviate HIV-related symptoms [12].

Among young Black MSM who self-report as seropositive, heavy marijuana users, as compared to never users, have been found to be significantly more likely to be unaware of their seropositive status (aOR 4.18; 95% CI 1.26, 13.89; adjusting for age, education, employment, insurance status, housing stability, depressive symptoms, alcohol use, and other substance use). However, no significant differences were found between heavy, intermittent, and non-users in regard to other stages of care

including linkage to care, retention in care, adherence to care, and viral suppression [34].

In another cohort of young black MSM, marijuana non-use was not found to be associated with engagement in care as compared to marijuana users; however, marijuana non-use was associated with no missed visits in the past 12 months (aOR 2.49; 95% CI 1.14, 5.44; $p = 0.02$). There were no significant associations between marijuana use and ARV uptake, self-reported adherence, or viral suppression [35].

Among adult MSM participating in the Multicenter AIDS Cohort Study (MACS), those who engaged in daily marijuana use were found to be less likely to have durable viral suppression (OR = 0.68 [0.46, 0.99]), as compared to non-users. However, after multivariate analyses adjusting for age, gender, race, housing other substance use, and depressive symptoms, no significant differences were found in durable viral suppression between users (daily and less than daily) and non-users [36]. Further, among MSM in the early MACS cohort (recruited before 2001), a positive HIV serostatus was significantly associated with a higher prevalence of current and daily marijuana use.

Discussion

Due to the shifting landscape of marijuana-related policies and legislation, it is critically important to assess how marijuana impacts outcomes along the HIV continuum of care. While estimates vary across samples, one study indicated that approximately 25% of HIV-infected adults report current marijuana use compared to only 6.7% of their uninfected counterparts [8•]. The purpose of this review was to examine recent studies that assess the relationship between marijuana use and the HIV continuum of care. The majority of studies focused on adherence to ARV therapy. The small number of studies demonstrated a link between marijuana use, especially current heavy use, and HIV-positive status. However, there were no clear and consistent associations between marijuana use and retention in HIV treatment and adherence to ARV medications.

Although marijuana use is associated with HIV-positive status [24], recent studies suggest marijuana use does not reduce immune function [26] and is not associated with increased mortality risk [25] among HIV-infected individuals. However, there are some data to indicate that marijuana use may be associated with other complications (e.g., memory impairment; [17•]). Thus, interventions focused on minimizing the harms of marijuana use (e.g., developing cannabis use disorder), while also recognizing that some HIV-infected individuals may use marijuana to address HIV-related side effects, may be most useful for this population, even among those using medicinal marijuana. This is especially important for HIV-

infected individuals, as they have been shown to use prescription marijuana well above their prescribed dose [e.g., 12, 22]. Thus, future research is needed to identify the optimal dose of marijuana that reduces negative symptoms without causing impairment or distress.

HIV-infected individuals are increasingly using marijuana for medical purposes in addition to recreationally. One reason HIV-infected individuals are using medical marijuana is to reduce the negative side effects of ARV treatments [12, 22]. Thus, future research could investigate the effectiveness of medical marijuana in reducing the negative side effects of ARV, while also minimizing factors that reduce HIV treatment adherence among marijuana users. At this point, little is known about how and why marijuana use impacts HIV treatment adherence for some but does not for others. Given this conflicting evidence, there is need for research identifying mechanisms of marijuana's impact on HIV treatment adherence to inform the development of targeted interventions as suggested by Kipp and colleagues [27].

Alternatively, if it is not an option to receive medical marijuana or medical marijuana is contraindicated and the goal is to encourage abstinence from marijuana among HIV-infected individuals, then research examining reasons for marijuana use among HIV-infected individuals might be used to identify alternate approaches for meeting their needs. For example, common reasons for marijuana use among HIV-infected individuals include stress reduction and appetite stimulation [8•, 37, 38]. Thus, providing alternative methods for coping with stress and stimulating appetite, for example, could ostensibly help HIV-infected individuals achieve abstinence from marijuana.

The effect of marijuana use on ARV adherence remains inconclusive, with studies showing negative [39], positive [40], or no effect [41] of use on adherence and non-adherence. HIV-infected individuals may use marijuana to mediate HIV symptoms and medication side effects [39, 42, 43], and users have been shown to be more likely to be avoidant, avoid stressors, and negative experiences [44] which may contribute to medication non-adherence. Further, while substance use has consistently been shown to impact ARV adherence, there may be attributes of use (e.g., frequency) or treatment adherence (e.g., self-efficacy), as demonstrated by Gross and colleagues [30], that may be stronger predictors of associations between medication adherence and marijuana use.

Nearly 75% of a sample of young Black MSM in an urban area used marijuana, and those who used heavily were significantly more likely to be unaware of their HIV serostatus than intermittent and non-users [34]. However, there were no differences in regard to continuum of care outcomes, despite the likelihood that knowledge of status would impact seeking, and access to treatment (i.e.,

linkage to care), which would then ultimately influence viral suppression. It is possible that due to the relatively young age of the sample studied by Morgan and colleagues [34], a significant number of those youth with knowledge of their seropositive status may have been recently diagnosed and not yet engaged in care. Further, studies have shown high rates of medical mistrust and perceived racism among Black men [45, 46], which may universally impact linkage to care regardless of whether these individuals are substance-using or not.

In regard to viral load, there are preclinical studies that suggest that cannabinoids may reduce HIV viral load and replication [47, 48]; however, the literature in clinical studies remains inconclusive, with some studies indicating no differences [49], others showing HIV-infected, marijuana-using individuals having higher viral load [50] and yet others having lower viral load [51, 52]. These studies are subject to a number of limitation including small samples and lack of diversity within samples.

Future Research Directions

Studies remain unstandardized in their definitions of, and threshold for, marijuana use (e.g., frequency, duration of use), and few clinical studies have measured use in an objective manner. Furthermore, the form of marijuana used has not been systematically examined in HIV-infected samples and there are a lack of longitudinal studies that examine patterns of use and associated HIV care cascade outcomes across longer periods of time. Additionally, there remains little examination of differences between medicinal marijuana users and recreational users, such that different studies may be capturing different types or proportions of marijuana users, and motivation for marijuana use likely influences treatment adherence and other HIV care outcomes. It is likely that psychosocial factors, related to marijuana use among HIV-infected individuals, also impact treatment adherence and engagement in care. Subpopulations of HIV-infected individuals studied are also disparate in regard to personal and psychosocial characteristics, which may further affect the relationship between marijuana use and treatment.

Future research is needed to understand reasons for marijuana use among HIV-infected samples and to develop interventions focused on addressing potential negative consequences associated with marijuana use. Tailored intervention approaches that incorporate and address specific function(s) marijuana serves for an individual may be particularly useful. HIV care settings may consider delivery of interventions that can address problematic marijuana use in conjunction with other substance use and psychiatric comorbidity, particularly among patients who are poorly engaged in care or experience challenges adhering to their ARV medications. Medical providers within an HIV care

setting may also be better equipped to assess and address medical conditions that HIV-infected individuals are using marijuana medicinally to treat.

Last, the limited data regarding the relation between marijuana use and HIV care cascade outcomes highlight the potential for important differences in use by geographic location, race/ethnicity, age, and sexual orientation. Thus, further research to examine the extent to which patterns and reasons for marijuana use differ across subpopulations of HIV-infected individuals are needed. Such investigations could inform future prevention and treatment efforts to elucidate potential factors upon which interventions should be tailored.

Conclusions

This review of recent literature assessing the relationship between marijuana use and HIV continuum of care outcomes identified a small number of studies among diverse subgroups of HIV-infected individuals. The samples included adolescents and adults from community and HIV and substance abuse treatment settings within the USA. Despite the diversity in samples, findings consistently pointed to an association between heavy marijuana use and HIV-positive status, thereby highlighting a significant need for HIV testing among heavy marijuana users. Additional research is needed to disentangle the nuanced relationship between marijuana and HIV treatment engagement and adherence to ART medication, as well as linkage to care and viral suppression. Overall, this review highlights the need for more studies in this area, especially given the high prevalence of frequent marijuana use among subgroups of HIV-infected individuals and the common perception that marijuana reduces HIV-related symptoms. Understanding and addressing the influence of modifiable risk factors, such as marijuana use, at each stage of the care continuum are critical to providing optimal care and treatment for all HIV-infected individuals.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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