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MAJOR ARTICLE

# Cannabis Use Is Associated With Decreased Antiretroviral Therapy Adherence Among Older Adults With HIV

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***Background.*** Conflicting evidence exists on the impact of cannabis use on antiretroviral therapy (ART) adherence among people with human immunodeficiency virus (PWH). We leveraged data collected among older PWH to characterize longitudinal associations between cannabis use and ART adherence.

***Methods.*** AIDS Clinical Trials Group (ACTG) A5322 study participants were categorized as <100% (≥1 missed dose in past 7 days) or 100% (no missed doses) ART adherent. Participants self-reported current (past month), intermittent (past year but not past month), and no cannabis (in past year) use at each study visit. Generalized linear models using generalized estimating equations were fit and inverse probability weighting was used to adjust for time-varying confounders and loss to follow-up.

***Results.*** Among 1011 participants (median age, 51 years), 18% reported current, 6% intermittent, and 76% no cannabis use at baseline; 88% reported 100% ART adherence. Current cannabis users were more likely to be <100% adherent than nonusers (adjusted risk ratio [aRR], 1.53 [95% CI, 1.11–2.10]). There was no association between ART adherence and current versus intermittent (aRR, 1.39 [95% CI, .85–2.28]) or intermittent versus no cannabis use (aRR, 1.04 [95% CI, .62–1.73]).

***Conclusions.*** Among a cohort of older PWH, current cannabis users had a higher risk of <100% ART adherence compared to nonusers. These findings have important clinical implications as suboptimal ART adherence is associated with ART drug resistance, virologic failure, and elevated risk for mortality. Further research is needed to elucidate the mechanisms by which cannabis use decreases ART adherence in older PWH and to advance the development of more efficacious methods to mitigate nonadherence in this vulnerable population.

**Keywords.** adherence; aging; antiretroviral therapy; cannabis; HIV.

With consistent antiretroviral therapy (ART), people with human immunodeficiency virus (PWH) can successfully suppress plasma viral replication to nondetectable levels and experience improved health and quality of life. High ART adherence among PWH is critical, as significant health-related risks, such as development of ART resistance [1], virologic failure [2, 3], opportunistic infections [4], progression to AIDS [5], and mortality [6–8], have been associated with nonadherence. Moreover, less than perfect ART adherence has been associated with elevated inflammation, risk for viral rebound, and drug resistance mutations [9, 10]. Notably, with widespread ART use, more PWH are surviving into older age, and previous work has suggested that older PWH may be more likely to be adherent to their ART regimens as compared with younger PWH [11, 12]. However, given that factors particular to older PWH, such as severe menopausal symptoms [13] or greater neurocognitive impairment [14], are associated with ART nonadherence, an improved understanding of the challenges to adherence and development of methods by which to limit nonadherence is crucial, particularly among older PWH.

Multiple intersecting barriers likely underlie poor ART adherence among PWH, such as stigmatization, ART regimen complexities, negative side effects, neurocognitive impairment, and emotional factors, such as stress, depression, and anxiety [15–18]. Another salient factor that could drive ART nonadherence may be increased rates of substance use, which is

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highly prevalent among older PWH [19] and which may not only increase the risk for nonadherence to ART [20] but may also decrease the efficacy of ART treatment through drug–drug interactions [21]. Notably, the use of cannabis (*Cannabis sativa*) by PWH in the United States has been shown to be particularly high, ranging from 23% to 56% as compared to 13.3% in the general population [22]. Among participants in the AIDS Clinical Trials Group (ACTG) study A5322, a prospective observational study of PWH aged 40 years and older, 18% of participants were current cannabis users. Common reasons for cannabis use by PWH include reducing anxiety, depression, nausea, and pain and increasing appetite [23, 24]. However, cannabis use may have a detrimental impact on the medical care of PWH and may be associated with increased rates of missed clinic appointments [25]. Previous work has also shown that PWH with severe cannabis use disorder reported lower ART adherence [26] and more severe human immunodeficiency virus (HIV) symptoms and ART side effects as compared to cannabis-using and non-cannabis-using PWH without severe cannabis use disorder [27]. In contrast, conflicting evidence suggests that cannabis use has no impact on ART initiation, ART adherence, or plasma viral load suppression [28–30]. Moreover, although a prior study demonstrated that PWH who recently used cannabis had a significantly lower quality of life as compared to non-cannabis-using PWH, there was no difference in disease burden, physical function, $CD4^+$ T-cell count, or HIV plasma viral load between the 2 groups [31]. Importantly, the association of regular, current cannabis use with ART adherence in older PWH has not been well defined.

Due to the high prevalence of cannabis use among PWH and the unfavorable impacts that elevated cannabis use may have on ART adherence, greater knowledge of how regular cannabis consumption affects the care of PWH is critical. This is particularly important among older PWH, who may be more negatively affected by the adverse health-related effects of ART nonadherence as compared to younger PWH. Therefore, the goal of this study was to longitudinally evaluate associations between self-reported cannabis use and ART adherence among a cohort of older PWH. We hypothesized that individuals who regularly used cannabis would have a greater incidence of ART nonadherence as compared to those who intermittently used cannabis or were non–cannabis users.

## METHODS

### Study Population

This analysis used data from participants in the ACTG study A5322, also known as HAILO (HIV Infection, Aging, and Immune Function Long-Term Observational Study). ACTG A5322 was a multicenter (32 clinical research sites in the United States and Puerto Rico) prospective observational study of 1035 PWH aged ≥40 years enrolled between November 2013 and July 2014. Follow-up ended in December 2021. Semiannual evaluations included current medications and adherence; substance use questionnaires occurred annually. In the current analysis, A5322 participants with data on cannabis use and ART adherence available for at least 1 study visit from week 0 through week 288 of the study were considered for inclusion. We identified 1011 A5322 participants (98%) who fit these criteria and were included in the current analyses and excluded the 24 A5322 participants (2%) that did not fit these criteria. Among these participants, individual visits where an ART treatment gap lasted >21 days were excluded.

### Patient Consent Statement

All A5322 participants provided written informed consent before enrollment. A5322 was approved by the local institutional review board at each site.

### Cannabis

A5322 participants completed a yearly substance use questionnaire and self-reported cannabis use via a question that asked, "When was the last time you used marijuana (pot, hashish)?" by selecting 1 answer: (0) never used; (1) >1 year ago; (2) within the past year up until 1 month ago; or (3) within the past month. Participants were classified at each time point as nonusers if they answered (0) or (1), intermittent users if they answered (2), or current users if they answered (3).

### ART Adherence

Antiretroviral therapy adherence was assessed every 6 months via self-reported questionnaires. Participants were categorized as 100% adherent if they reported no missed doses of any medication within the past 7 days, and as <100% adherent otherwise. We selected <100% as our cutoff given previous findings that imperfect (eg, <100%) ART adherence is associated with significant biological ramifications, such as inflammation, which has been linked to elevated morbidity and mortality among PWH regardless of apparent plasma HIV suppression [9, 32]. Since cannabis use was measured yearly, only adherence obtained at the concomitant annual visits was used in the current analyses.

### Covariates

Based on epidemiological evidence from previous literature [26, 30], covariates considered as potential confounders included sex assigned at birth, age at baseline (A5322 study entry), race/ethnicity, educational level, health insurance, years on ART, nadir CD4, antidepressant use, physical activity level, alcohol use level, smoking status, other substance use, and comorbidities (Table 1). Potential confounders were refined by adding each separately to a univariable logistic regression model predicting ART adherence from cannabis use. Any variable

**Table 1. Baseline Characteristics by Cannabis Use**

| Characteristic | Cannabis Use | | | | | | Total (n = 1011) | |
|---|---|---|---|---|---|---|---|---|
| | Nonuser (n = 771) | | Intermittent User (n = 63) | | Current User (n = 177) | | | |
| Sex assigned at birth | | | | | | | | |
| Male | 605 | (78) | 58 | (92) | 154 | (87) | 817 | (81) |
| Female | 166 | (22) | 5 | (8) | 23 | (13) | 194 | (19) |
| Age, y | | | | | | | | |
| Median (Q1, Q3) | 51 | (46, 57) | 50 | (46, 58) | 49 | (44, 54) | 51 | (46, 56) |
| 40–49 | 329 | (43) | 27 | (43) | 91 | (51) | 447 | (44) |
| 50–59 | 321 | (42) | 22 | (35) | 68 | (38) | 411 | (41) |
| ≥60 | 121 | (16) | 14 | (22) | 18 | (10) | 153 | (15) |
| Race/ethnicity | | | | | | | | |
| White, non-Hispanic | 362 | (47) | 34 | (54) | 95 | (54) | 491 | (49) |
| Black, non-Hispanic | 225 | (29) | 22 | (35) | 57 | (32) | 304 | (30) |
| Hispanic or other | 184 | (24) | 7 | (11) | 25 | (14) | 216 | (21) |
| Education | | | | | | | | |
| High school graduate or less | 271 | (35) | 18 | (29) | 74 | (42) | 363 | (36) |
| Any education beyond high school | 500 | (65) | 45 | (71) | 103 | (58) | 648 | (64) |
| ART adherence | | | | | | | | |
| <100% | 76 | (10) | 12 | (19) | 37 | (21) | 125 | (12) |
| 100% | 695 | (90) | 51 | (81) | 140 | (79) | 886 | (88) |
| Time on ART, y | | | | | | | | |
| Median (Q1, Q3) | 8 | (4.5, 12.1) | 7 | (4.1, 11.3) | 7 | (4.1, 11.8) | 8 | (4.4, 12.0) |
| Nadir CD4 count, cells/μL | | | | | | | | |
| Median (Q1, Q3) | 184 | (56, 298) | 228 | (123, 323) | 213 | (78, 297) | 191 | (62, 300) |
| HIV-1 RNA, copies/mL | | | | | | | | |
| ≥50 | 60 | (8) | 5 | (8) | 11 | (6) | 76 | (8) |
| <50 | 708 | (92) | 58 | (92) | 165 | (94) | 931 | (92) |
| Comorbidities—any[a] | | | | | | | | |
| Yes | 132 | (17) | 11 | (17) | 26 | (15) | 169 | (17) |
| No | 639 | (83) | 52 | (83) | 151 | (85) | 842 | (83) |
| Medical insurance | | | | | | | | |
| None/unknown | 159 | (21) | 11 | (17) | 29 | (16) | 199 | (20) |
| Public | 184 | (24) | 22 | (35) | 53 | (30) | 259 | (26) |
| Private | 343 | (44) | 21 | (33) | 69 | (39) | 433 | (43) |
| Medicare | 85 | (11) | 9 | (14) | 36 | (15) | 120 | (12) |
| Antidepressant use—any[b] | | | | | | | | |
| Yes | 151 | (20) | 16 | (25) | 51 | (29) | 218 | (22) |
| No | 620 | (80) | 47 | (75) | 126 | (71) | 793 | (78) |
| Physical activity | | | | | | | | |
| <3 d/wk | 360 | (48) | 28 | (47) | 77 | (44) | 465 | (47) |
| ≥3 d/wk | 389 | (52) | 31 | (53) | 97 | (56) | 517 | (53) |
| Alcohol use[c] | | | | | | | | |
| Abstainer | 342 | (45) | 15 | (25) | 27 | (15) | 384 | (38) |
| Light drinker | 279 | (37) | 22 | (36) | 75 | (43) | 376 | (38) |
| Moderate drinker | 41 | (5) | 2 | (3) | 21 | (12) | 64 | (6) |
| Heavy drinker | 100 | (13) | 22 | (36) | 53 | (30) | 175 | (18) |
| Smoking status[d] | | | | | | | | |
| Never | 367 | (48) | 16 | (25) | 31 | (18) | 414 | (41) |
| Prior | 250 | (32) | 20 | (32) | 70 | (40) | 340 | (34) |
| Current | 154 | (20) | 27 | (43) | 76 | (43) | 257 | (25) |
| Substance use—any[e] | | | | | | | | |
| Never | 561 | (73) | 22 | (35) | 74 | (43) | 657 | (65) |

**Table 1. Continued**

| Characteristic | Cannabis Use | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Nonuser (n = 771) | | Intermittent User (n = 63) | | Current User (n = 177) | | Total (n = 1011) | |
| Prior | 182 | (24) | 30 | (48) | 69 | (40) | 281 | (28) |
| Current | 27 | (4) | 11 | (17) | 31 | (18) | 69 | (7) |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; HIV-1, human immunodeficiency virus type 1; Q1, quartile 1; Q3, quartile 3.

[a]Comorbidities (cardiovascular disease, hypertension, diabetes, cancer [incident or within 5 years], combined liver disease, kidney disease, or chronic hepatitis C) were tested individually and combined.

[b]Antidepressant use was tested by class (selective serotonin reuptake inhibitors, aminoketone class, heterocyclics, tricyclics) and combined.

[c]Alcohol use levels are defined for participants assigned male sex at birth (M) or female sex at birth (F) based on reported drinks per week: abstainer, zero drinks; light drinker, <7 (M) or <3 (F) drinks per week and no binging; moderate drinker, 7–14 (M) or 3–7 (F) drinks per week and no binging; heavy drinker, >14 (M) or >7 (F) drinks per week or binging. Binging is defined as ≥5 drinks on 1 occasion in the last 30 days.

[d]Smoking status: never, no use; prior, if the participant has a history of smoking cigarettes; current, if the participant smokes cigarettes currently.

[e]Substance use includes use of any of the following: cocaine, heroin, amphetamines, or other nonprescribed prescription drug. Substance use levels: never, no use; prior, use >1 month ago; or current, within the past month.

that changed the coefficient (log odds) for the effect of cannabis use on the outcome by ≥10% was considered a confounder.

### Statistical Analysis

Generalized linear models using generalized estimating equations (GEEs) were used to estimate the association between cannabis use and ART adherence at the same study visit. The models employed the logistic link and binomial distribution to estimate risk ratios (RRs). Time was modeled as study weeks, and the independence structure was used to reduce GEE bias from time-dependent confounding [33]. Sex assigned at birth and an interaction term for time-sex were included to assess whether the effect of cannabis use differed by sex assigned at birth. A separate model included age (<50 or ≥50 years) and a time-age interaction term to assess whether the effect of cannabis use differed by age.

Inverse probability weighting (IPW) was used to control for time-varying confounders and loss to follow-up. A comprehensive description of the methodology for creating IPWs can be found elsewhere [34, 35]. For this analysis, stabilized inverse probability of treatment (cannabis use group) weights (IPTWs) were calculated as the probability of treatment given baseline covariates (sex assigned at birth, race/ethnicity, educational level, smoking status, time on ART, cannabis use history) divided by the probability of treatment given baseline and time-varying covariates (alcohol use, other substance use, ART adherence history). Probabilities were estimated with multinomial logistic regression models. Stabilized inverse probability of censoring weights (IPCWs) were calculated by fitting logistic regression models with the same predictors as for the IPTW models, but with only the most recent visit's cannabis use and previous visit's data (rather than the current visit) for time-varying exposures. The final stabilized IPWs were the product of the IPTW and IPCW. They were then truncated to the 1st and 99th percentiles and used in the generalized linear models.

Due to their cumulative nature, IPW creation requires full model data for each visit. Multiple imputation was used to impute missing covariates. For missed visits, data were imputed using the last observation carried forward, or for data missing from week 0, the next observation carried backwards. Only observed visits were used in the final generalized linear models. All data analysis was completed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

## RESULTS

### Study Population Characteristics

The 1011 (98%) participants who completed at least 1 substance use questionnaire while on ART and were included in the current analyses contributed 1–7 time points with a median (Q1, Q3) of 6 (4, 7). The majority of participants were assigned male sex at birth (81% [n = 817]) and the median age at baseline was 51 years (Table 1). Gender identity data were not collected from A5322 participants. Additionally, 49% (n = 491) of participants identified as White non-Hispanic, 30% (n = 304) identified as Black non-Hispanic, and 21% (n = 216) identified as Hispanic or as another race or ethnicity (Table 1).

### Baseline Characteristics by Cannabis Use

At baseline there were 177 current cannabis users (18%), 63 intermittent cannabis users (6%), and 771 non–cannabis users (76%) (Table 1). A greater proportion of cannabis users reported using antidepressants as compared to intermittent and non–cannabis users; more participants reported being light or heavy drinkers among intermittent and current cannabis users. A higher frequency of non–cannabis users reported abstaining from alcohol and other substances and being tobacco never-smokers as compared to intermittent and current cannabis users. Groups were similar in terms of educational level, time on ART, nadir CD4 count, percentage undetectable viral load,

comorbid conditions, medical insurance coverage, and physical activity level. Among study participants, 12% (n = 125) were classified at baseline as being less than 100% adherent to their ART regimens (Table 1). A higher proportion of <100% ART adherence was observed among current cannabis users (21% [n = 37]) and intermittent cannabis users (19% [n = 12]) than non–cannabis users (10% [n = 76]).

#### Association Between Cannabis Use and Poor ART Adherence

In GEE models IP-weighted for study dropout only, current cannabis users were more likely to be <100% ART adherent than nonusers (RR, 1.78 [95% confidence interval {CI}, 1.42–2.23]; $P < .01$; Figure 1). There was no association between current versus intermittent cannabis use (RR, 1.29 [95% CI, .85–1.96]; $P = .22$) or intermittent versus non–cannabis use and ART adherence (RR, 1.38 [95% CI, .91–2.07]; $P = .13$). In multivariable analyses that were adjusted for baseline covariates and IP-weighted for time-varying exposures and study dropout, the association between cannabis use versus nonuse and <100% ART adherence remained (adjusted RR [aRR], 1.53 [95% CI, 1.11–2.10]; $P < .01$). There was no evidence for an interaction between age and current versus non–cannabis use.

#### Relationship Between Cannabis Use and ART Adherence by Sex Assigned at Birth

Among participants assigned male sex at birth, we observed that current cannabis users were more likely to be <100% ART adherent than nonusers in dropout-weighted (RR, 1.77 [95% CI, 1.38–2.27]; $P < .01$) and fully adjusted models (aRR, 1.67 [95% CI, 1.20–2.35]; $P < .01$) (Figure 2). An association between current cannabis use and <100% ART adherence among participants assigned female sex at birth as compared to nonusers was also observed in the dropout-weighted model (RR, 2.27 [95% CI, 1.29–4.01]; $P < .01$), but not in the fully adjusted model (aRR, .89 [95% CI, .42–1.89]; $P = .70$) (Figure 2). This interaction was not statistically significant ($P = .12$).

## DISCUSSION

Herein, we found that current cannabis users have a higher risk of being <100% adherent to their ART regimen when compared to nonusers, consistent with most previous work [26, 27]. Importantly, this association was maintained even when adjusted for demographic and behavioral characteristics. However, to our knowledge, our work is among the first to show this relationship specifically among older PWH, in which engagement in medical care and successful ART adherence is particularly important. Indeed, although ART adherence among older PWH is generally better as compared to younger PWH [11], factors particular to older PWH, such as severe menopausal symptoms [13] or enhanced neurocognitive impairment [14], are associated with ART nonadherence. Thus, a better understanding of how exogenous factors like cannabis use may interact with other determinants of ART nonadherence among older PWH is critical, given the unique risks and challenges that older PWH may experience.

Nonadherence to ART has historically been associated with poor outcomes, with early regimens requiring >95% adherence for successful virologic outcomes [4]. However, more modern ART regimens are associated with viral suppression when adherence is at ≥85% [36], thought to be due to the pharmacologic forgiveness offered by these regimens [37]. Alternatively, previous work demonstrated that less than perfect adherence was associated with elevated inflammatory markers, including

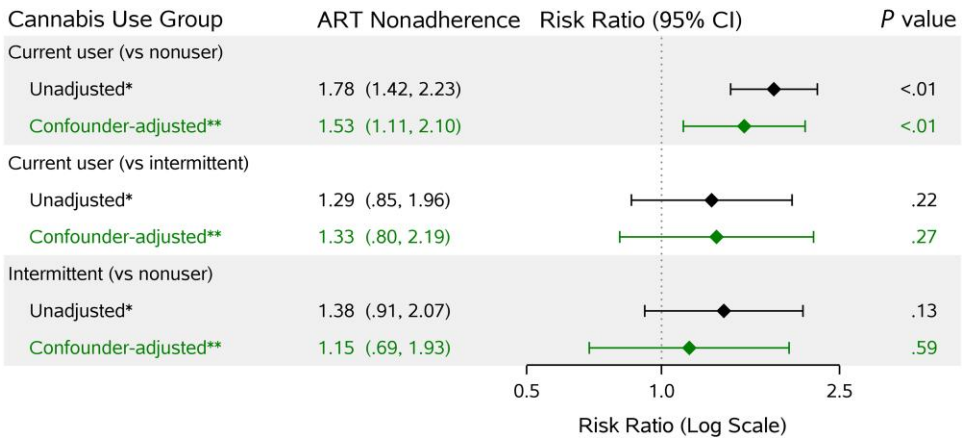


**Figure 1.** Associations between cannabis use and antiretroviral therapy (ART) adherence among older people with human immunodeficiency virus. Generalized linear models using generalized estimating equations were used to estimate the association between cannabis use and ART adherence. Data are depicted as a forest plot of the nonadherence risk ratio (RR with 95% confidence interval [CI]). *Inverse probability (IP)–weighted for dropout. **Adjusted for baseline covariates (sex, race/ethnicity, educational level, smoking status, time on ART, cannabis use history) and IP-weighted for dropout and time-varying exposures (alcohol use, other substance use, ART adherence history).

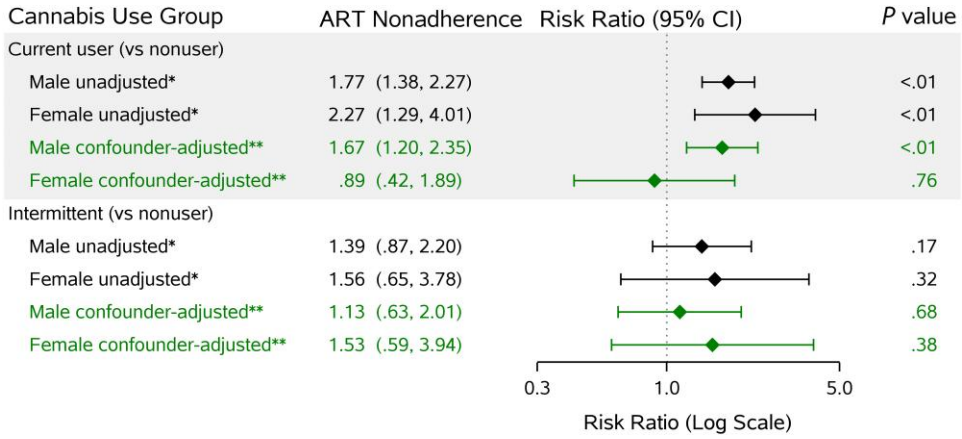


**Figure 2.** Relationship between cannabis use and antiretroviral therapy (ART) adherence by sex assigned at birth. Models that included interaction terms for time × sex assigned at birth were used to evaluate whether the association between cannabis use and ART adherence varied among participants by sex assigned at birth. Data are depicted as a forest plot of the nonadherence risk ratio (RR with 95% confidence interval [CI]). *Inverse probability (IP)–weighted for dropout. **Adjusted for baseline covariates (race/ethnicity, educational level, smoking status, time on ART, cannabis use history) and IP-weighted for dropout and time-varying exposures (alcohol use, other substance use, ART adherence history).

interleukin-2, interleukin-6, and interleukin-10, interferon-γ, tumor necrosis factor–α, and C-reactive protein, although this finding was largely driven by those with adherence <85% [9]. Moreover, in the setting of nondetectable viremia, less than perfect adherence, as measured by tenofovir-diphosphate or emtricitabine-triphosphate concentrations in dried blood spots, was a prognosticator of viral rebound, while intermittent adherence led to drug resistance mutations [10, 38, 39]. Combined, these data reinforce the need for high adherence to ART in PWH, as well as to understand factors such as the reasons for cannabis use that underlie nonadherence.

It is possible that sex-specific effects of cannabis exposure could constitute a potential mechanism underlying our observation that males but not females with current cannabis use were less likely to be ART adherent. Indeed, females and males differ in terms of cannabinoid receptor expression, cannabinoid metabolism, subjective effects of cannabis, and anxiety and depressive symptoms associated with cannabis use, among others [40, 41]. Notably, a prior study conducted among women enrolled in the Women's Interagency HIV Study (WIHS) demonstrated a significant effect of cannabis use on suboptimal ART adherence when restricted to single-tablet ART [26]. Although the women in A5322 and WIHS were similar in terms of race and ethnicity, other characteristics differed between these cohorts, including alcohol and substance use. These and other differences between male and female study participants, such as with sociodemographic characteristics, may impose distinct challenges and pressures that influence the specific reasons for and effects of cannabis use. A more precise understanding of the pharmacokinetic, physiological, behavioral, socioeconomic, and gender identity variations between participants by sex at birth will be critical to delineate the mechanisms underlying differences in the associations between cannabis use and ART adherence across cohorts.

Although our findings suggest that current cannabis use is associated with less than complete ART adherence, additional literature suggests that cannabis use may be associated with beneficial immune effects, distinct from ART. For example, regular cannabis use by PWH has been associated with lower blood-brain barrier permeability as compared to PWH with less than daily use of cannabis [42]. Moreover, cannabis use was associated with faster decay of HIV DNA in PWH as compared to non–cannabis use [43] and lower plasma viremia following seroconversion [44]. Additionally, PWH with heavy cannabis use had lower peripheral inflammation and cellular immune activation as compared to non-cannabis-using PWH [45]. Similarly, recent cannabis use by PWH was associated with reduced levels of soluble inflammatory markers in blood and cerebrospinal fluid [46]. Data on the associations between cannabis use and levels of proinflammatory cytokines are mixed [47]. Thus, these findings underscore the importance of understanding how the potentially beneficial effects of cannabis use could be leveraged to offset inflammation due to HIV infection while minimizing any direct deleterious consequences on ART adherence or psychosocial or cognitive functioning.

A major strength of the current study was our ability to adjust for demographic and behavioral elements that are well-established risk factors for ART adherence. An additional strength was the use of data from a large cohort of older PWH who were followed longitudinally. A caveat of this may be that because all participants were enrolled in longitudinal clinical studies, our current study reflects a higher level of adherence to medication and clinical care than other study

populations, which may limit the generalizability of our findings. Likewise, participation in a clinical study and access to clinical care may have led to a greater awareness among our study participants of the current ambiguity surrounding the benefits versus consequences of cannabis use, which may have contributed to the lower percentage of cannabis users in our study population as compared to what has been previously observed (18% vs 23%–56% [22], respectively). A limitation of our study is that because A5322 did not collect the number of days with imperfect ART adherence, we were unable to assess whether <85% adherence as compared to <100% adherence may be impacted by cannabis use. A further limitation of our study was the underrepresentation of women, which could explain the nonsignificant relationship between cannabis use and adherence among women, as well as the nonsignificant interaction by sex. Moreover, the small number of intermittent cannabis users precludes our ability to understand relationships between intermittent cannabis use and adherence. Our study was also limited in that our measurements of cannabis use were self-reported, and on an annual basis. Although self-reported cannabis use is a widely used measure, it is possible that inaccurate self-reporting could have influenced the outcomes. Additionally, controlling for other substance use specifically by each substance could have been more informative than a control for other substance use. Taken together, future studies that include both a greater number of women and participants that represent variable levels of cannabis use are needed. Moreover, studies that incorporate quantification of cannabis metabolites as objective measures of cannabis use could help to confirm self-reported cannabis usage, enable the measurement of the extent of cannabis use by each participant, allow for more precise classification of study participants into cannabis use categories, explore the differential effects of various types of cannabis products, and allow for evaluation of potential dose-response relationships [45, 48].

An additional limitation of our study is that since A5322 did not collect data on cannabis use indication, we were not able to distinguish between medical and recreational cannabis use. Common reasons for poor ART adherence among PWH include ART regimen complexities, negative side effects including nausea, and emotional factors such as anxiety and depression [15–17]. Notably, reduction of stress, anxiety, depression, physical pain, and nausea are among the most cited reasons for cannabis use among PWH [23, 24]. Conflicting evidence exists as to whether cannabis use for symptom management among PWH may provide a potential behavioral link with effective ART adherence, with some studies suggesting no association [30, 49] and others finding a significant impact [27, 50]. Additional work is needed to determine whether behavioral reasons, such as cannabis use for symptom management, may underlie our observed link between cannabis use and lower ART adherence among older PWH.

Taken together, our findings suggest that regular cannabis use by older PWH is associated with a greater risk of imperfect ART adherence compared to non–cannabis use. These findings have important clinical implications for the care of older PWH, as even a small reduction in ART adherence has been linked with greater inflammation and a higher risk for drug resistance, less effective viral suppression, and mortality. A better understanding of the relationship between cannabis use and ART adherence among older PWH can facilitate the development of more efficacious methods by which to mitigate nonadherence in this particularly vulnerable population. Finally, future work is needed to elucidate how the adverse effects of cannabis use on ART adherence could be balanced against the potential beneficial uses of cannabis to reduce inflammation and immune activation in older PWH.

## Notes

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