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Self-Reported Cannabis Use and Markers of Inflammation in Men Who Have Sex With Men With and Without HIV

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Abstract

Background: Chronic inflammation contributes to aging and organ dysfunction in the general population, and is a particularly important determinant of morbidity and mortality among people with HIV (PWH). The effect of cannabis use on chronic inflammation is not well understood among PWH, who use cannabis more frequently than the general population.

Materials and Methods: We evaluated participants in the Multicenter AIDS Cohort Study (MACS) beginning in 2004 with available data on cannabis use and inflammatory biomarkers. Associations of current cannabis use with plasma concentrations of inflammatory markers were adjusted for hepatitis C, tobacco smoking, and comorbidities. Markers were analyzed individually and in exploratory factor analysis (EFA).

Results: We included 1352 men within the MACS. Twenty-seven percent of HIV-negative men, 41% of HIV viremic men, and 35% of virologically suppressed men reported cannabis use at baseline. Among cannabis users, 20–25% in all groups defined by HIV serostatus were daily users, and the same proportion reported weekly use. The remaining $\sim$50% of users in all groups reported monthly or less frequent use. Four biomarker groupings were identified by EFA: *Factor 1*: immune activation markers; *Factor 2*: proinflammatory cytokines; *Factor 3*: Th1- and Th2-promoting cytokines; and *Factor 4*: inflammatory chemokines. In EFA, daily users had 30% higher levels of Factor 2 biomarkers than nonusers ($p = 0.03$); this was the only statistically significant difference by cannabis use status. Among individual markers, concentrations of IL-1β, IL-2, IL-6, and IL-8 (Factor 2); IL-10 (Factor 3); and BAFF (Factor 1) were higher ($p < 0.05$) among daily cannabis users than among nonusers, after adjusting for HIV serostatus and other covariates.

Discussion: Associations between daily cannabis use and proinflammatory biomarker levels did not differ by HIV serostatus. Further prospective studies with measured cannabis components are needed to clarify the impact of these compounds on inflammation. Our findings can facilitate for hypothesis generation and selection of biomarkers to include in such studies.

Keywords: HIV; inflammation; CBD; THC; cannabis; inflammatory biomarkers

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Introduction

Chronic inflammation is a well-recognized contributor to aging and progressive organ damage in the general population, and this effect appears to be more pronounced in people with HIV (PWH).[1,2] Although AIDS development can now be effectively prevented or reversed by combination antiretroviral therapy (cART), PWH continue to suffer from degenerative disorders, organ dysfunction, and malignancies earlier in life than their HIV-uninfected counterparts; much of this can be attributed to persistently higher levels of chronic inflammation and resulting in systemic damage in addition to immune exhaustion (senescence).[3–5]

Although levels of inflammation are lower among PWH with greater adherence to cART, they do not typically normalize to levels as low as observed among HIV-uninfected individuals.[6,7] As PWH age and the burden of inflammation-related comorbidities increases, novel strategies are needed to decrease levels of inflammation and their clinical sequelae.

Cannabis is the most commonly used psychoactive substance in the United States with an estimated 26 million people > 12 years of age currently utilizing it,[8,9] and recent trends toward its legalization suggest increased recreational and therapeutic use.

A Cochrane review and meta-analysis of 79 trials including 6462 participants reported that, among other outcomes, moderate-quality evidence supported the benefit of cannabinoids for chronic pain, and that low-quality evidence suggests improvements in nausea and vomiting, weight gain in HIV infection, all of which are conditions over-represented in PWH. In this study, cannabinoids were associated with an increased risk of short-term adverse events (e.g., dizziness, dry mouth, confusion, and disorientation).[10]

The long-term health risks and benefits of cannabis use, including effects on chronic inflammation, have not been sufficiently studied in humans.[11] Furthermore, the effects of cannabis use among PWH remain unclear: several studies have suggested that individual cannabinoids naturally occurring in the cannabis plant can attenuate chronic inflammation and interfere with HIV replication itself.[12–15] However, other studies point toward reduced cART adherence among regular cannabis users and an association of cannabis use with polysubstance use, both of which contribute to poorer HIV-related and overall health outcomes.[16,17]

Two analyses from the Multicenter AIDS Cohort Study (MACS) have reported a higher risk for cardiovascular events and pulmonary conditions among self-reported cannabis users, particularly among men with HIV.[18,19] Our understanding of the independent effects of cannabis among PWH is incomplete, in part, because reasons for cannabis use are diverse. Cannabis may be utilized for treatment of anxiety, depressive symptoms, neuropathic or other types of pain, as well as ART-associated side effects (e.g., nausea or lack of appetite), many of which have also been reported as reasons for lower ART adherence.[20–22]

In this analysis, we examined the association between self-reported current cannabis use and concentrations of inflammatory biomarkers among MACS participants with and without HIV, accounting for other individual characteristics known, or suspected to have an effect on inflammation.

Materials and Methods

Study design and population

The MACS is an ongoing prospective cohort study of HIV infection among men who have sex with men and is conducted at four sites in the United States: Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA/Columbus, OH.[23] Men in the cohort are evaluated at study visits every 6 months that include standardized interviews, physical examinations, and collection of biological samples for laboratory analysis and storage. MACS study protocols at all sites were approved by their local institutional review boards and all participants provided informed consent before enrollment and before any new procedure.

The study population for this analysis consisted of all MACS men contributing a study visit beginning in 2004, where both measurement of plasma inflammatory biomarker concentrations and self-reported cannabis use were collected. The 2004 cutoff was used to maximize the inclusion of men with HIV treated with modern cART. For each participant, we selected the first eligible visit after 2004.

Exposure, outcome, and covariate ascertainment

Cannabis use since the previous study visit (within the prior 6 months) was assessed by self-report, and in those reporting such use, the frequency was characterized as daily, weekly, monthly, or less than monthly. Monthly and less than monthly were collapsed into a single category for analysis.

As previously described, BAFF, sCD14, sCD27, gp130, sIL2-Ra, sIL-6R, sTNFR2, CXCL10, GM-CSF, IL-1β, IL-2, IL-6, TNF-α, IL-8, CCL4, IL-10, IL-12p70, CCL11, CCL2, and CCL13 were measured

from stored plasma using the MesoScale Discovery (MSD, Gaithersburg, MD) and Luminex (Luminex, Austin, TX) platforms.[5] C-reactive protein (CRP) was measured with an immunonephelometric assay by a clinical reference laboratory (Quest Diagnostics, Madison, NJ).

CD4+ T cell counts (cells/μL) were assessed with flow cytometry. Plasma HIV-1 RNA (viral load) was measured with the Roche Amplicor assay, sensitive to 50 copies/mL. Infection with hepatitis C virus (HCV) was defined as the presence of detectable HCV RNA. Diabetes mellitus was defined by hemoglobin A1C $>6.5\%$, a fasting glucose of ≥ 126 mg/dL, or self-reported use of antidiabetes medication. Anemia was defined by a hemoglobin concentration below the fifth percentile in the general population. Obesity was defined by a body mass index ≥ 30 kg/m^2. Tobacco smoking was collected by self-report.

Statistical analysis

Crude differences in biomarker concentrations between and among cannabis use groups were assessed with the Wilcoxon rank sum and Kruskal–Wallis tests. In this cross-sectional study, the causal relationship between cannabis use and inflammation might be viewed as directed either way; in conceptualizing the analysis, we considered cannabis use as the exposure of interest and inflammatory biomarker concentrations as the outcomes. Because biomarker concentrations exhibited heterogeneous distributions, we modeled them as generalized gamma to avoid imposing strong distributional assumptions. In multivariable models, as previously done with these biomarker levels in other MACS analyses, we held scale (σ) and shape (λ) parameters constant and allowed the location parameter β to vary by covariates, which allows one to interpret the effect of a covariate as a constant percentage shift of the distribution across percentiles.[24] We adjusted multivariable models for measured covariates that were plausible confounders of the cannabis–inflammation relationship: HIV serostatus, age, race, HCV infection, smoking, obesity, diabetes, and anemia. Statin use was not a significant predictor of biomarker concentrations and was, therefore, not included in adjusted models. To adjust for multiple significance tests, we controlled the false discovery rate at 5% using the Benjamini–Hochberg procedure.[25]

To parsimoniously capture the covariance structure of the 24 biomarkers, we employed exploratory factor analysis (EFA) using the same methods as Wada et al.[1] In EFA, underlying "factors" are assumed to give rise to the covariance structure among observed variables. We used iterative principal factor extraction and selected four factors through the use of a scree plot. Factor rotation was orthogonal, using the Varimax method. Each individual was assigned a score for each factor based on his observed biomarker concentrations. Factor scores were created using Bartlett's method, which is unbiased with independent exposure variables and latent outcomes.[26] We then fit multivariable linear regression models to model each factor score as a function of cannabis use frequency and possible confounding variables. We used SAS v9.4 (Cary, NC) and Stata 11 (College Station, TX) for all analyses.

Results

Characteristics of study population

The study population comprised 1352 men from the MACS (281 HIV-uninfected men, 464 men with detectable HIV-1 RNA ["viremic"], and 607 men with undetectable HIV-1 RNA ["suppressed"]) who contributed study visits from 2004 to 2009; their characteristics are displayed in Table 1. Among all participants, 73% reported ever using cannabis; 27% of HIV-uninfected men, 41% of viremic men, and 35% of suppressed men reported cannabis use at the index visit. Among all cannabis users (uninfected, viremic, and suppressed), 20–24% were daily users, 24–26% reported weekly use, and $\sim 50\%$ reported monthly or less frequent use.

Individual biomarker analyses

Individual biomarker concentrations across groups defined by HIV serostatus are displayed in Table 2. Significant unadjusted differences in biomarker concentrations between cannabis nonusers and daily users were detected in the following: HIV-uninfected cannabis daily users had higher concentrations of IL-2 than HIV-uninfected nonusers; viremic cannabis daily users had higher levels of GM-CSF, IL-1β, IL-2, and IL-8 than viremic nonusers; and suppressed daily users had higher concentrations of IL-12p70, CCL11, and IL-8 than suppressed nonusers.

In adjusted regression models, compared with nonusers, cannabis daily users had significantly higher concentrations of BAFF, IL-1β, IL-2, IL-6, IL-8, and IL-10 (Fig. 1 and Appendix Table A1). Only levels of IL-1β, which were 54% higher among cannabis users than nonusers, remained significant when adjusting for multiple tests by controlling the false discovery rate at 5%. There were no significant differences in these results by HIV serostatus or virological suppression group.

Table 1. Characteristics of Study Population

	HIV uninfected ($n=281$)	People with HIV, viremic ($N=464$)	People with HIV, suppressed HIV-1 RNA ($n=607$)	Total ($n=1352$)
Cannabis use reported	27%	41%	35%	36%
Daily	23%	20%	24%	23%
Weekly	25%	24%	26%	25%
Monthly	14%	17%	13%	15%
<Monthly	38%	39%	37%	38%
Ever used cannabis	72%	75%	73%	73%
Age (years)	48 (42, 56)	46 (40, 51)	48 (42, 54)	47 (41, 53)
Body mass index (kg/m^2)	26.1 (23.4, 29.3)	24.5 (22.6, 27.3)	24.6 (22.6, 27.3)	24.9 (22.7, 27.6)
Black, non-Hispanic	37%	38%	23%	31%
White, Hispanic	4%	6%	7%	6%
White, non-Hispanic	53%	46%	60%	54%
Other race	7%	8%	9%	8%
Cigarette smoking at visit	42%	41%	31%	37%
Statin use	14%	15%	31%	22%
Aspirin use	30%	23%	30%	28%
Hepatitis C infection	21%	12%	9%	13%
Diabetes	14%	13%	14%	14%
Anemia	10%	25%	16%	18%
Hypertension	25%	19%	21%	21%
Prior cancer diagnosis	2%	6%	7%	6%
Any prior cART exposure	—	76%	99%	89%
No cART at visit	—	53%	10%	32%
Prior AIDS diagnosis	—	13%	14%	14%
CD4+ T cell count (cells/μL)	—	380 (243, 561)	578 (415, 758)	490 (331, 676)
CD4+ nadir (cells/μL)	—	280 (156, 411)	269 (146, 383)	272 (152, 392)
HIV-1 viral load (RNA copies/mL)	—	9514 (887, 46,500)	40 (40, 40)	40 (40, 4346)
Years since diagnosis	—	13.3 (7.5, 18.6)	15.4 (11.8, 18.4)	14.7 (9.9, 18.4)
Years since cART initiation	—	6.3 (4.0, 7.9)	6.5 (3.9, 8.2)	6.5 (3.9, 8.1)

Values reported as number (frequency) or median (interquartile range).
cART, combination antiretroviral therapy.

Exploratory factor analysis

EFA identified four factors, each characterized by biomarkers with high loadings (defined by convention as >0.4). Four biomarkers (CRP, CXCL13, IFN-γ, and CCL17) did not load within the prespecified range for any of the four identified factors. The factors corresponding to distinct immunological processes (detailed in the discussion) are listed hereunder.

1. *Factor 1* (BAFF, sCD14, sCD27, gp130, sIL2-Ra, sIL-6R, sTNFR2, and CXCL10): immune activation markers.
2. *Factor 2* (GM-CSF, IL-1β, IL-2, IL-6, TNF-α, IL-8, and CCL4): predominantly proinflammatory cytokines.
3. *Factor 3* (IL-10, IL-12p70): Th1- and Th2-promoting cytokines secreted by regulatory B cells (Bregs) and T cells (Tregs) (IL-10), and by dendritic cells and macrophages (IL-12p70).
4. *Factor 4* (CCL11, CCL2, and CCL13): inflammatory chemokines.

We next incorporated factor scores rather than individual biomarkers into regression analyses (Table 3). Daily cannabis users had significantly higher scores for Factor 2 relative to nonusers, after adjustment for HIV serostatus or virological suppression group and other covariates (0.3 standard deviations higher, $p<0.05$). No other statistically significant associations were observed between cannabis use frequency and inflammatory factor scores.

Discussion

In this analysis of men with and without HIV, we found a significant association between cannabis use and inflammatory biomarker concentrations that grouped in our *Factor 2* subset of inflammatory markers, as well as BAFF (*Factor 1*) and IL-10 (*Factor 3*). We did not find that these associations differed by HIV serostatus, after accounting for other inflammatory comorbidities and characteristics.

An interesting finding deserving further discussion pertains to the association of reported cannabis use with IL-10. IL-10 is regarded as an anti-inflammatory Th2-pathway cytokine operative in dampening inflammation in the gut, improving risk of atherosclerosis and postmyocardial infarction healing, and in immune tolerance during pregnancy. A combination of CBD–THC (but not THC or CBD alone) has been reported

Table 2. Distributions of Biomarker Concentrations by HIV Serostatus and Cannabis Users or Nonusers

	HIV uninfected		People with HIV, detectable HIV-1 RNA		People with HIV, suppressed HIV-1 RNA	
	Median (IQR)		Median (IQR)		Median (IQR)	
Cannabis use group	Nonusers	Users	Nonusers	Users	Nonusers	Users
BAFF (pg/mL)	1950 (1714, 2245)	1953 (1653, 2275)	2346 (1882, 3046)	2363 (1910, 3115)	2099 (1785, 2577)	2091 (1758, 2584)
CCL11 (pg/mL)	1679 (1256, 2394)	1522 (1055, 2497)	1557 (1121, 2233)	1677 (1250, 2288)	***1749 (1234, 2440)***	***1927 (1348, 2737)***
CCL13 (pg/mL)	846 (618, 1044)	802 (540, 1072)	781 (566, 1041)	775 (620, 1048)	838 (648, 1137)	847 (642, 1159)
CCL17 (pg/mL)	557 (408, 823)	483 (321, 815)	511 (318, 768)	544 (327, 851)	537 (340, 834)	586 (369, 953)
CCL2 (pg/mL)	514 (382, 683	536 (321, 667)	555 (406, 739)	593 (426, 758)	562 (405, 725)	571 (416, 733)
CCL4 (pg/mL)	145 (92, 208)	154 (99, 216)	109 (77, 160)	119 (86, 159)	137 (93, 189)	144 (103, 202)
CRP (mg/dL)	1.00 (0.50, 2.85)	0.90 (0.30, 2.00)	1.50 (0.70, 3.45)	1.50 (0.80, 3.550	1.30 (0.60, 3.25)	1.50 (0.70, 3.80)
CXCL10 (pg/mL)	153 (102, 239)	143 (90, 287)	468 (248, 744)	386 (231, 715)	225 (145, 340)	204 (135, 343)
CXCL13 (pg/mL)	290 (237, 347).	287 (249, 3610	340 (267, 402)	345 (280, 413)	281 (231, 334)	279 (229, 330)
GM-CSF (pg/mL)	0.72 (0.47, 1.22)	0.74 (0.58, 1.31)	***0.55 (0.41, 0.89)***	***0.63 (0.44, 1.20)***	0.66 (0.45, 1.11)	0.65 (0.47, 1.11)
IFN-γ (pg/mL)	1.17 (0.74, 1.71)	1.19 (0.92, 1.76)	1.55 (1.05, 2.38)	1.46 (0.88, 2.26)	1.21 (0.80, 1.81)	1.23 (0.81, 1.69)
IL-10 (pg/mL)	3.11 (1.76, 6.38)	3.36 (2.08, 8.00)	3.66 (2.31, 5.78)	3.65 (2.34, 6.16)	2.53 (1.69, 4.20)	2.69 (1.78, 4.65)
IL-12p70 (pg/mL)	2.13 (1.05, 5.92)	2.30 (1.33, 6.62)	1.78 (1.16, 3.29)	1.92 (1.00, 3.82)	***1.46 (0.83, 2.98)***	***1.79 (1.00, 3.89)***
IL-1β (pg/mL)	0.40 (0.23, 0.64)	0.45 (0.29, 0.74)	***0.34 (0.23, 0.59)***	***0.41 (0.28, 0.75)***	0.36 (0.25, 0.63)	0.38 (0.25, 0.64)
IL-2 (pg/mL)	***0.56 (0.38, 0.89)***	***0.64 (0.42, 1.29)***	***0.64 (0.39, 1.01)***	***0.71 (0.46, 1.24)***	0.56 (0.38, 0.96)	0.58 (0.38, 1.04)
IL-6 (pg/mL)	0.99 (0.70, 1.51)	1.09 (0.61, 1.66)	1.11 (0.73, 1.74)	1.20 (0.76, 1.87)	1.02 (0.66, 1.87)	1.04 (0.71, 1.65)
IL-8 (pg/mL)	13.86 (9.69, 19.25)	14.25 (9.44, 29.78)	***13.15 (9.22, 22.44)***	***15.55 (10.32, 30.98)***	***13.71 (9.39, 24.33)***	***15.98 (10.98, 29.28)***
sCD14 (mg/dL)	2.08 (1.82, 2.49)	2.13 (1.87, 2.48)	2.56 (2.08, 3.09)	2.50 (2.15, 2.99)	2.60 (2.17, 3.07)	2.59 (2.17, 3.23)
sCD27 (pg/mL)	9273 (7800, 12,049)	9668 (7993, 11,245)	15,374 (11,957, 20,706)	15,288 (11,962, 20,755)	10,273 (8311, 13,458)	10,640 (8156, 12,783)
sGP130 (mg/dL)	0.25 (0.23, 0.29)	0.24 (0.22, 0.29)	0.26 (0.23, 0.30)	0.26 (0.23, 0.30)	0.28 (0.24, 0.32)	0.26 (0.24, 0.31)
sIL-2Rα (pg/mL)	1421 (1144, 1739)	1391 (1119, 1691)	1933 (1477, 2529)	2021 (1389, 2670)	1374 (1081, 1883)	1461 (1157, 1817)
sIL-6R (pg/mL)	49,573 (40,418, 62,372)	47,848 (39,699, 57,676)	50,148 (42,554, 61,751)	50,234 (41,218, 63,036)	48,759 (39,801, 58,457)	46,542 (37,895, 54,870)
sTNFR2 (pg/mL)	2404 (1974, 3076)	2292 (1969, 2688)	3519 (2692, 4876)	3511 (2708, 4645)	2580 (2079, 3444)	2666 (2025, 3283)
TNF-α (ptag/mL)	8.78 (7.06, 11.16)	7.92 (6.34, 10.14)	12.52 (9.36, 17.61)	12.98 (8.96, 18.34)	9.08 (7.35, 12.63)	9.74 (7.51, 14.59)

Bold italics indicate significant ($p < 0.05$) differences between cannabis users and nonusers from Wilcoxon rank sum test.
IQR, interquartile range.

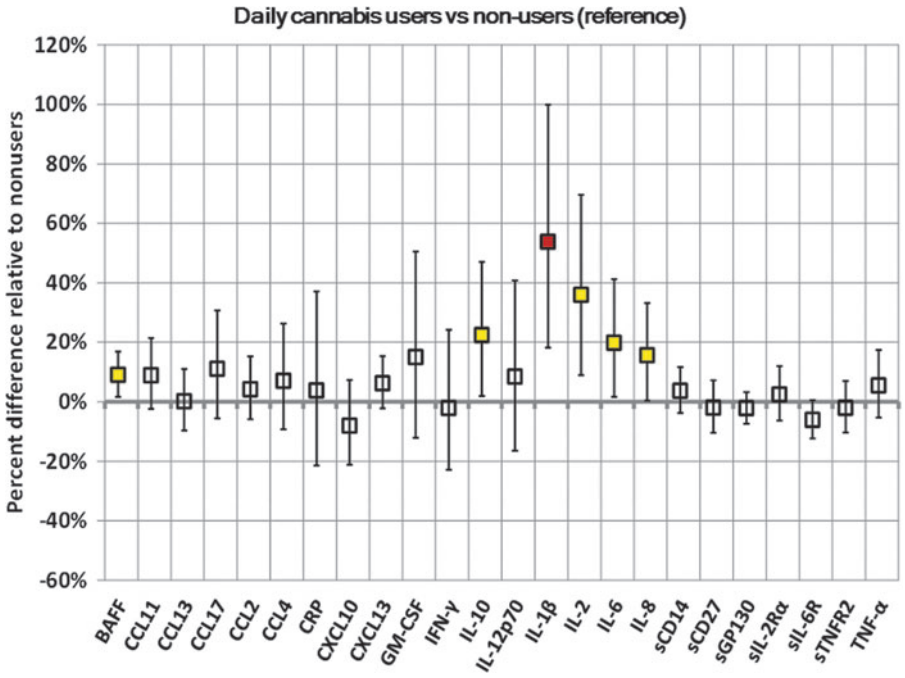

FIG. 1. Results from multivariable generalized gamma regression demonstrating the effect of cannabis daily use versus nonuse on markers of inflammation and immune activation. Models are adjusted for HIV serostatus, age, race, HCV infection, cigarette smoking, obesity, diabetes, and anemia. Squares indicate adjusted estimates and bars indicate 95% confidence intervals; yellow indicates significance of $p < 0.05$ before adjusting for multiple comparisons, red indicates significance after adjusting for multiple tests by controlling false discovery rate at 5%. HCV, hepatitis C virus.

to decrease inflammation in experimental autoimmune encephalomyelitis by increasing IL-10 levels, while also decreasing proinflammatory cytokines, including TNF-α, IL-1β, IL-6 (our *Factor 2*), among others.[27] Interestingly, cannabinoid 2 receptor-specific cannabinoid has been proposed as potentially beneficial for improved transplanted graft survival by promoting IL-10-related pathways.[28]

Several limitations of our study should be noted, including the cross-sectional approach and the inclusion of only men. The self-reported use of cannabis as a measurement of exposure lacks nuance and accuracy, particularly with respect to the concentrations of delta-9-THC and CBD. These components of cannabis may have differential effects on inflammatory marker responses, and historically, during the period of these data collection, CBD has not been as prominently present in various cannabinoids containing products as it is today.

Although we demonstrated an association with increased IL-1β and IL-6 levels among self-reported daily cannabis users, it is not clear whether these elevated levels could be a predisposing condition or the result of high-THC/low-CBD cannabis consumption. For instance, CBD has been shown to decrease the production and inhibit the release of these markers in a recent study of 23 individuals in Colorado that reported that subjects who used a strain of cannabis that contained both THC and CBD had lower levels of proinflammatory biomarkers, including TNF-α, IL-1β, and IL-6 than subjects who used a strain with a high THC content and minimal CBD.[29]

To improve upon the findings of our study, precise measurements of cannabinoid, flavonoid, and terpenoid exposure can be done by liquid or gas chromatography paired with mass spectrometry in biological samples.[30–32] Understanding the magnitude of exposure to these cannabis components paired with pre- and postexposure measurements of the same battery of inflammatory markers may add to the understanding of cannabinoids' mediation as pertaining to the

Table 3. Differences in Distributions of Latent Inflammatory Factors Associated with Cannabis Use from Multivariable Generalized Gamma Regressions Among People With and Without HIV

	Beta	*p*	95% LL	95% UL
Factor 1				
Monthly or less	−0.093	0.186	−0.230	0.045
Weekly	−0.029	0.773	−0.228	0.169
Daily	−0.069	0.521	−0.280	0.142
Factor 2				
Monthly or less	0.097	0.281	−0.079	0.272
Weekly	0.150	0.245	−0.103	0.404
Daily	0.302	0.028	0.032	0.571
Factor 3				
Monthly or less	0.089	0.274	−0.070	0.247
Weekly	0.116	0.323	−0.114	0.345
Daily	0.205	0.099	−0.039	0.448
Factor 4				
Monthly or less	0.091	0.286	−0.076	0.258
Weekly	−0.149	0.224	−0.390	0.091
Daily	0.080	0.537	−0.175	0.336

Factor 1 (BAFF, sCD14, sCD27, gp130, sIL2-Ra, sIL-6R, sTNFR2, and CXCL10): immune activation markers. *Factor 2* (GM-CSF, IL-1β, IL-2, IL-6, TNF-α, IL-8, and CCL4): predominantly proinflammatory cytokines. *Factor 3* (IL-10 and IL-12p70): Th1- and Th2-promoting cytokines secreted by regulatory B cells (Bregs) and T cells (Tregs) (IL-10), and by DCs and macrophages (IL-12p70). *Factor 4* (CCL11, CCL2, and CCL13): inflammatory chemokines.

DCs, dendritic cells; 95% LL, lower bound of 95% confidence limit; 95% UL, upper bound of 95% confidence limit.

inflammatory responses. EFA in a prospective study may identify biological pathways affected by these compounds. Improved understanding would be helpful in designing studies of objective outcomes, such as the effects of cannabinoids on the development of fibrosis/sclerosis within various organ systems and related morbidity and mortality.

Conclusions

Although we found an association between cannabis use and some inflammatory pathways, we did not find that the effects of cannabis on inflammation differed by HIV serostatus. The effects of specific doses, route of exposure, and combinations of cannabinoids on measured outcomes require further study to better understand the short- and long-term consequences of cannabis use among adults both with and without HIV, and selection of biomarkers for future studies may now be informed by the cross-sectional associations reported here. Such efforts would be particularly timely now since current sales of cannabis-containing products continue to be driven mostly by anecdotal evidence of benefit or, more commonly, by the recreational psychoactive properties of THC.[11,33,34] Further knowledge of the therapeutic potential of cannabinoids can help elucidate additional benefits as well as potential risks associated with their prolonged use in these settings.[35–37]

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References

1. Wada NI, Bream JH, Martinez-Maza O, et al. Inflammatory biomarkers and mortality risk among HIV-suppressed men: a multisite prospective cohort study. Clin Infect Dis. 2016;63:984–990.
2. Erlandson KM, Allshouse AA, Campbell TB, et al. Association of functional impairment with inflammation and immune activation in HIV type 1-infected adults receiving effective antiretroviral therapy. J Infect Dis. 2013;208:249–259
3. Deeks SG, Verdin E, McCune JM. Immunosenescence and HIV. Curr Opin Immunol. 2012;24:501–506.
4. Freund A, Orjalo AV, Desprez P, Campisi J. Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med. 2010;16: 238–246.
5. Appay V, Kelleher AD. Immune activation and immune aging in HIV infection. Curr Opin HIV AIDS. 2016;11:242–249.
6. Wada NI, Jacobson LP, Margolick JB, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS. 2015;29:463–471.
7. Castillo-Mancilla JR, Brown TT, Erlandson KM, Wada NI, et al. Suboptimal adherence to combination antiretroviral therapy is associated with higher levels of inflammation despite HIV suppression. Clin Infect Dis. 2016;63:1661–1667.
8. Substance Abuse and Mental Health Services Administration (SAMHSA). 2017 National Survey on Drug Use and Health (NSDUH) Annual Report. Available at https://www.samhsa.gov/data/report/2017-nsduh-annual-national-report (last accessed June 6, 2019).
9. Hughes, A., Lipari, R.N., and Williams, M.R. Marijuana use and perceived risk of harm from marijuana use varies within and across states. The CBHSQ report: July 26, 2016. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD, 2016.
10. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313:2456–2473.
11. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. The National Academies Press, Washington, DC, 2017.
12. Rom S, Persidsky Y. Cannabinoid receptor 2: potential role in immunomodulation and neuroinflammation. J Neuroimmune Pharmacol. 2013;8: 608–620.
13. Williams JC, Appelberg S, Goldberger BA, et al. Delta9-THC treatment during human monocyte differentiation reduces macrophage susceptibility to HIV-1 infection. J Neuroimmune Pharmacol. 2014;9:369–379.
14. Manuzak JA, Gott TM, Kirkwood JS, et al. Heavy cannabis use associated with reduction in activated and inflammatory immune cell frequencies in antiretroviral therapy-treated human immunodeficiency virus-infected individuals. Clin Infect Dis. 2018;66:1872–1882.
15. Costantino CM, Gupta A, Yewdall AW, et al. Cannabinoid receptor 2-mediated attenuation of CXCR4-tropic HIV infection in primary CD4+ T cells. PLoS One. 2012;7:e33961
16. Bon-Miller MO, Oser ML, Bucossi, Trafton JA. Cannabis use and HIV antiretroviral therapy adherence and HIV related symptoms. J Behav Med. 2014;37:1–10.
17. Peretti-Watel P, Spire B, Lert F, Obadia Y. Drug use patterns and adherence to treatment among HIV-positive patients: evidence from a large sample of French outpatients (ANRS-EN12-VESPA 2003). Drug Alcohol Depend. 2006;82:S71–S79.
18. Lorenz DR, Dutta A, Mukerji SS, et al. Marijuana use impacts midlife cardiovascular events in HIV-infected men. Clin Infect Dis. 2017;65:626–635.
19. Lorenz DR, Uno H, Wolinsky SM, Gabuzda D. Effect of marijuana smoking on pulmonary disease in HIV-infected and uninfected men: a longitudinal cohort study. EClinicalMedicine. 2019. https://doi.org/10.1016/j.eclinm.2019.01.003
20. Al-Dakkak I, Patel S, Maiese EM, et al. The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: a systematic review and meta-analysis. AIDS Care. 2013;25:400–414.
21. Prentiss D, Power R, Israelski DM, et al. Petterns of marijuana use among paitents with HIV/AIDS followed in a public health care setting. J Acquir Immune Defic Syndr. 2004;35:38–45.
22. D'Souza G, Matson PA, Wilson TE, et al. Medicinal and recreational marijuana use among HIV-infected women in the Women's Interagency HIV Cohort (WIHS), 1994–2010. J Acquir Immune Defic Syndr. 2012;61:618–626.
23. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol. 1987;126:310–318.
24. Cox C, Chu H, Schneider MF, Muñoz A. Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution. Stat Med. 2007;26:4352–4374.
25. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B. 1995;57: 289–300.
26. Bartlett MS. Properties of sufficiency and statistical tests. Proc R Soc Lond A Math Phys Sci. 1937;160:268–282.
27. Al-Ghezi ZZ, Miranda K, Nagarkatti M and Nagarkatti PS. Combination of cannabinoids, Δ9-tetrahydrocannabinol and cannabidiol, ameliorates experimental multiple sclerosis by suppressing neuroinflammation through regulation of miRNA-mediated signaling pathways. Front Immunol. 2019;10:1921.
28. Robinson RH, Meissler JJ, Fan X, et al. A CB2-selective cannabinoid suppresses T-cell activities and increases Tregs and IL-10. J Neuroimmune Pharmacol. 2015;10:318–332.
29. Bidwell LC, Mueller R, York Williams SL, et al. A novel observational method for assessing acute responses to cannabis: preliminary validation using legal market strains. Cannabis Cannabinoid Res. 2018;3:35–44.
30. Raikos N, Schmid H, Nussbaumer S, et al. Determination of D9-tetrahydrocannabinolic acid A (D9-THCA-A) in whole blood and plasma by LC–MS/MS and application in authentic samples from drivers suspected of driving under the influence of cannabis. Forensic Sci Int. 2014;243:130–136.
31. Paul R, Williams R, Hodson V, Peake C. Detection of cannabinoids in hair after cosmetic application of hemp oil. Sci Rep. 2019;9:2582.
32. Luo YR, Yun C, Lynch KL. Quantitation of cannabinoids in breath samples using a novel derivatization LC–MS/MS assay with ultra-high sensitivity. J Anal Toxicol. 2019;43:331–339.
33. Buckner JD, Shah SM, Dean KE, et al. Cannabis use frequency and use-related impairment among African American and White users: the impact of cannabis use motives. Ethn Health. 2016;21:318–331.
34. Dai H, Richter KP. A national survey of marijuana use among US adults with medical conditions, 2016–2017. JAMA Netw Open. 2019;2:e1911936.
35. De Ternay J, Naassila M, Nourredine M, et al. Therapeutic prospects of cannabidiol for alcohol use disorder and alcohol-related damages on the liver and the brain. Front Pharmacol. 2019;10:627.
36. Turna J, Syan SK, Frey BN, et al. Cannabidiol as a novel candidate alcohol use disorder pharmacotherapy: a systematic review. Alcohol Clin Exp Res. 2019;43:550–563.
37. Wang Y, Mukhopadhyay P, Cao Z, et al. Cannabidiol attenuates alcohol induced liver steatosis, metabolic dysregulation, inflammation and neutrophil-mediated injury. Sci Rep. 2017;7:12064.

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Abbreviations Used

95% LL = lower bound of 95% confidence limit
95% UL = upper bound of 95% confidence limit
CBD = cannabidiol
cART = combination antiretroviral therapy
CRP = C-reactive protein
DCs = dendritic cells
EFA = exploratory factor analysis
HCV = hepatitis C virus
IQR = interquartile range
MACS = Multicenter AIDS Cohort Study
PWH = people with HIV
THC = tetrahydrocannabinol

(*Appendix follows* →)

Appendix

Appendix Table A1. Differences in Distributions of Inflammatory Biomarker Concentrations Associated with Daily Cannabis Use (Compared with No Use) from Multivariable Generalized Gamma Regressions

Biomarker	% Shift	95% LL	95% UL	*p*	*q*
BAFF	9.0%	1.7%	16.9%	0.015	0.006
CCL11	8.9%	−2.4%	21.4%	0.127	0.017
CCL13	0.1%	−9.7%	11.0%	0.981	0.050
CCL17	11.1%	−5.6%	30.7%	0.206	0.021
CCL2	4.2%	−5.9%	15.2%	0.430	0.035
CCL4	7.0%	−9.3%	26.3%	0.420	0.033
CRP	3.8%	−21.4%	37.1%	0.794	0.046
CXCL10	−8.1%	−21.2%	7.3%	0.285	0.023
CXCL13	6.2%	−2.3%	15.4%	0.155	0.019
GM-CSF	15.0%	−12.1%	50.5%	0.308	0.025
IFN-γ	−2.2%	−22.9%	24.1%	0.857	0.048
IL-10	22.4%	1.9%	47.0%	0.031	0.008
IL-12p70	8.4%	−16.5%	40.8%	0.543	0.038
IL-1β	53.8%	18.2%	99.9%	***0.001***	0.002
IL-2	35.9%	8.9%	69.6%	0.007	0.004
IL-6	19.8%	1.6%	41.2%	0.031	0.010
IL-8	15.6%	0.4%	33.1%	0.044	0.013
sCD14	3.7%	−3.7%	11.6%	0.341	0.029
sCD27	−2.0%	−10.5%	7.2%	0.658	0.044
sGP130	−2.2%	−7.4%	3.2%	0.418	0.031
sIL-2Rα	2.4%	−6.3%	12.0%	0.601	0.040
sIL-6R	−6.1%	−12.4%	0.5%	0.070	0.015
sTNFR2	−2.1%	−10.4%	7.0%	0.643	0.042
TNF-α	5.4%	−5.3%	17.4%	0.334	0.027

Models are adjusted for HIV serostatus, age, race, HCV infection, cigarette smoking, obesity, diabetes, and anemia. *q*-Values for controlling false discovery rate at 5%; bold italics indicate *p*-value < *q*-value.

95% LL, lower bound of 95% confidence limit; 95% UL, upper bound of 95% confidence limit; HCV, hepatitis C virus.