Title

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Journal

JAIDS Journal of Acquired Immune Deficiency Syndromes, 83(1)

ISSN

1525-4135

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Publication Date

2020

DOI

10.1097/qai.0000000000002211

Peer reviewed

HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2020 January 01; 83(1): 56–64. doi:10.1097/QAI.0000000000002211.

Cannabis Exposure is Associated with a Lower Likelihood of Neurocognitive Impairment in People Living with HIV

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Abstract

Background: Aging and HIV have adverse effects on the CNS, including increased inflammation and neural injury, and confer risk for neurocognitive impairment (NCI). Prior research suggests the non-acute neurocognitive effects of cannabis in the general population are adverse or null. However, in the context of aging and HIV, cannabis use may exert beneficial effects due to its anti-inflammatory properties. In the current study, we examined the independent and interactive effects of HIV and cannabis on NCI, and the potential moderation of these effects by age.

Methods: Participants included 679 people living with HIV (PLHIV) and 273 people living without HIV (HIV−) (18-79 years old) who completed neurocognitive, neuromedical, and substance use assessments. NCI was defined as demographically-corrected global deficit score ≥0.5. Logistic regression models examined the effects of age, HIV, cannabis (history of cannabis substance use disorder and cannabis use in past year), and their two-way and three-way interactions on NCI.

Results: In logistic regression models, only a significant interaction of HIV X cannabis was detected (p=0.02). Among PLHIV, cannabis was associated with a lower proportion of NCI (OR=0.53, 95%CI=0.33–0.85), but not among HIV− individuals (p=0.40). These effects did not vary by age.

Conclusion: Findings suggest cannabis exposure is linked to a lower odds of NCI in the context of HIV. A possible mechanism of this result is the anti-inflammatory effect of cannabis, which may be particularly important for PLHIV. Further investigations are needed to refine the effects of

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Presented at the International Neuropsychological Society (INS) Annual Meeting; New York, NY (2019, February).

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

dose, timing, and cannabis compound on this relationship, which could inform guidelines for cannabis use among populations vulnerable to cognitive decline.

Keywords

Cannabis; Marijuana Use; HIV/AIDS; NeuroAIDS; Cognition; HIV associated neurocognitive disorders

Introduction

The advent of combination antiretroviral therapy (cART) has allowed people living with HIV (PLHIV) who have stable access to HIV treatment to achieve life expectancies near those without HIV[1]. Despite medical advancements, neurocognitive impairment (NCI) remains prevalent, affecting 25-50% of PLHIV[2,3], with highest rates among older PLHIV[4,5]. Older age and HIV infection are each independently associated with central nervous system (CNS) injury, including increased inflammation and subsequent neural damage[6,7]. Together, aging with HIV appears to inflict additive, or possible synergistic, detrimental effects on the CNS, leading to substantially increased risk for NCI[8,9]. Clinically, NCI among PLHIV is associated with impairments in everyday functioning (e.g., medication management)[10,11] that can impact progression of HIV, subsequent transmissibility, and even confer increased risk for early mortality. Thus, understanding factors that may increase risk for or resilience against NCI among PLHIV is vital to maintaining optimal health in this population.

Cannabis use/exposure represents one modifiable behavioral factor worthy of investigation as an agent of NCI risk or resilience. Cannabis use is highly prevalent among PLHIV, with self-reported use in the past year almost three times greater than that of the general population in the United States (U.S.)[12]. Many PLHIV report use of cannabis to ameliorate symptoms of HIV/AIDS such as neuropathic pain, nausea, mood problems, and appetite and weight loss[13,14]. Among older adults, medicinal cannabis use has also increased as state-based legalization of medical and recreational cannabis has expanded in the U.S.[15,16]. Among the numerous recent studies examining chronic effects (i.e., “residual” effects observed in the absence of acute intoxication) of cannabis use on neurocognition in the general population, results are highly inconsistent. Although large scale reviews indicate that the most consistent adverse effects of cannabis use are on verbal learning and memory[17,18], chronic effects on all other neurocognitive domains (e.g., executive function) vary widely by study, with many reporting no differences between cannabis users and non-users. A meta-analysis reported no residual negative effect of cannabis use on any neurocognitive domain after 25 days of abstinence[19], suggesting that some previous conclusions about permanence of adverse cannabis effects on cognition might not have sufficiently adjusted for recency of use. Some variations in neurocognitive outcomes may be potentially explained by relevant factors that differ within and across studies, such as amount of cannabis use, type and potency of cannabis exposure, and the context of use (e.g., age of use; concurrently with other substances; in the presence of HIV disease or other medical conditions). These potential moderating factors are understudied, and their examination may support possible conditional effects of cannabis use on neurocognitive function[20].

For example, previous research has shown that in certain conditions known to have detrimental effects on cognition (e.g., methamphetamine use; schizophrenia), cannabis exposure does not compound these detrimental effects, and may even be associated with reduced risk for NCI[21,22]. While there is some evidence that cannabis exposure may reduce neural injury by decreasing excitotoxicity and neuroinflammation[23,24], studies examining this in the context of HIV disease and the downstream neurocognitive effects of cannabis use are sparse and inconsistent, with reported effects ranging from adverse to protective[25-27]. Furthermore, we are unaware of any studies examining chronic effects of cannabis on neurocognition in the context of HIV and aging. Given the current literature, one plausible hypothesis is that in the context of aging and HIV (two processes in which inflammation plays a role), cannabis exposure will relate to better cognitive outcomes compared to younger PLHIV and HIV− older adults without cannabis exposure.

The current study examined the combined impact of cannabis, HIV, and aging on cognition. The first aim was to examine rates of NCI across four groups categorized by HIV status and cannabis exposure (CAN+; CAN−). We hypothesized (a) among HIV− groups, NCI rates will not differ between cannabis groups, while (b) among PLHIV groups, the CAN+ group will have lower rates of NCI compared to the CAN− group. In our second aim, we examined whether the effects of HIV or cannabis exposure on NCI were moderated by age in a model controlling for relevant predictors of NCI. We hypothesized we would detect a three-way age X HIV X cannabis interaction such that cannabis exposure would relate to less NCI among younger and older PLHIV, but the magnitude of the association would be greater among older PLHIV, and cannabis exposure would be unrelated to NCI among younger and older HIV− individuals. In our third study aim, we examined the effects of cannabis exposure by cognitive domain among any groups showing differential relationships between cannabis exposure and NCI in study aim two.

Methods

Participants and Design.

Participants included 952 community-dwelling adults (PLHIV n=679; HIV− n=273) enrolled in various NIH-funded research protocols at the University of California San Diego's HIV Neurobehavioral Research Program (HNRP, https://hnrp.hivresearch.ucsd.edu/), and include the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, HIV Neurobehavioral Research Center (HNRC) study, and NeuroAIDS study. Study details have been published elsewhere[28-30]. Study visits took place between 1998-2016 with 70.8% of visits after 2005. Exclusion criteria for the parent studies included history of non-HIV-related neurological, medical or psychiatric disorders that affect brain function (e.g., schizophrenia, traumatic brain injury, epilepsy), learning disabilities, or a dementia diagnosis. Exclusion criteria for the current analyses also included (1) any non-cannabis substance use disorder in the past year (2) positive urine toxicology for illicit drugs (except cannabis) or positive breathalyzer test for alcohol during study visits. Given the high rates of major depressive disorder (MDD) among PLHIV, estimated to range from 5-20%[31,32], the current study had no exclusions for current or past MDD in order to increase

generalizability of findings. UCSD's Human Research Protections Program approved all study procedures, and all participants provided written informed consent.

Demographic Evaluation.

Demographic information (age, years of education, sex/gender, race, and ethnicity) was obtained via self-report. Race and ethnicity were ascertained following NIH guidelines and consistent with the US Census Bureau methodology[33].

Substance Use and Psychiatric Evaluation.

To evaluate current and past histories of substance use disorders (alcohol, cannabis, cocaine, methamphetamine, opioid, sedative, hallucinogen) and major depressive disorder (MDD), the Composite International Diagnostic Interview (CIDI, v2.1) was administered. The CIDI is a computer-assisted, fully-structured interview that provides an assessment of alcohol, drug, and mental disorders using DSM–IV criteria[34]. Study methodology was developed prior to the release of the DSM–5, and thus, DSM–IV criteria are used in assessment in order to maintain consistency of diagnoses across multiple longitudinal cohorts in our large research center. In accordance with DSM–IV criteria, substance abuse was met when participants endorsed substance use despite recurring problems (e.g. interpersonal, work-related, physically hazardous, legal) that result from substance use, and substance dependence was met when participants endorsed experiencing symptoms of tolerance, withdrawal, and inability to control or cut down substance use[35]. For each substance, abuse and dependence criteria were combined into one substance use disorder variable, consistent with previous studies that attempt to capture more than one definition of substance misuse[36], and to be more consistent with current DSM–5 criteria and terminology. Lifetime total days and quantity of cannabis use were also assessed via a modified timeline follow-back (TLFB) interview[37]. This modified TLFB assesses average quantities and frequencies of use during participant-identified periods in their life (e.g., from age 20 to 23, age 23 to 28), starting from age of first use. These estimates are totaled to obtain an estimate of total lifetime days of use and total lifetime quantity of use. Although these are rough estimates, previous studies from our group have found distinct differences between estimates obtained from individuals who meet criteria for substance use disorders and those who do not[38,39].

Cannabis exposure (CAN+) was defined as individuals with both a history of cannabis use disorder and cannabis use in the past year, in order to capture individuals with both substantial past use and recent exposure. Those in the no-cannabis exposure group (CAN−) had no history of cannabis use disorder and no cannabis use in the past year. Thus, individuals in this group may have had past cannabis exposure, but it was remote and not severe. Furthermore, any individuals in the CAN− group whose lifetime average grams per day of cannabis use exceeded one gram were excluded.

Neuromedical Evaluation.

All participants underwent a comprehensive neuromedical assessment. Detailed medical and antiretroviral (ARV) usage history was captured via a structured, clinician-administered questionnaire. HIV infection was diagnosed by enzyme-linked immunosorbent assay with Western blot confirmation. Duration of HIV disease was determined by date since first

positive HIV test. Routine clinical chemistry panels, complete blood counts, rapid plasma reagin, hepatitis C virus antibody, and CD4+ T cells (flow cytometry) were performed. Levels of HIV viral load in plasma and CSF were measured using reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostics, Indianapolis, IN), with a lower limit of quantitation (LLQ) of 50 copies/ml. HIV viral load was dichotomized as detectable vs. undetectable at the LLQ of 50 copies/ml.

Neuropsychological Evaluation.

All participants completed neurocognitive tests of verbal fluency, executive function, processing speed, learning, delayed recall, working memory/attention, and motor skills. Specific tests that comprise each domain are displayed in Table 1. Raw test scores were transformed into normally-distributed T-scores (M=50; SD=10) which are demographically adjusted for age, education, sex/gender, and race/ethnicity based on published normative samples of HIV− participants[40,41]. Cognitive domain summary T-scores were generated by averaging T-scores across tests within a cognitive domain. T-scores for each test were also converted into deficit scores that ranged from 0 (T>40; no impairment) to 5 (T<20; severe impairment). Deficit scores are averaged across all tests to obtain a Global Deficit Score (GDS)[42,43]. GDS is therefore weighted to characterize severity of impairment, and is not influenced by any exceptionally high test scores (study sample range: 0—3.8). Consistent with prior studies, NCI was dichotomized using a validated cut-point of GDS ≥ 0.5[43,44], a score that represents performance that is at least mildly impaired on at least half of the tests.

Statistical Analyses.

Participants were categorized into four groups based on HIV status and cannabis exposure (HIV−/ CAN−, HIV−/CAN+, PLHIV/CAN−, PLHIV/CAN+). Assumptions for parametric methods were checked. Group differences on demographic, psychiatric, substance use, and disease characteristics were examined using ANOVA or Wilcoxon tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Pair-wise comparisons were examined using Tukey's HSD for continuous outcomes and Bonferroni-adjustments for dichotomous outcomes. Differences in cannabis exposure (CAN+ vs. CAN −) by HIV status and various demographic groupings (e.g., age, sex/gender, race/ethnicity, sexual orientation) were also examined using Chi-square statistics.

Any variables that both differed between the four HIV/CAN groups at $p<0.05$ and related to NCI at $p<0.05$ were included as covariates when examining the relationships between age, HIV, and cannabis exposure on NCI. Criteria for covariates led to the inclusion of race/ethnicity, current MDD, and past methamphetamine use disorder in our models. None of the HIV disease characteristics differed by cannabis exposure, and thus were not included as covariates.

For the first study aim, we examined rates of NCI across the four HIV/CAN groups with Chi-square tests unadjusted for covariates. For the second study aim, we used a data-driven approach to examination of a potential three-way interaction in a multivariate logistic regression model. Modeling our dichotomous NCI outcome as a function of age, HIV, cannabis exposure, and relevant covariates, we initially included a full factorial three-way

interaction between age X HIV X cannabis and all lower-order two-way interactions (age X HIV, age X cannabis, and HIV X cannabis). We then systematically removed any non-significant interactions from our model for a final analytic model. Age was treated as a continuous variable. For the third study aim, we examined the effect of cannabis exposure on seven cognitive domain T-scores in separate multivariable linear regression models among groups showing differential cannabis-NCI relationships in study aim two, and including relevant covariates. *p* values for the association of cannabis exposure with each cognitive domain were adjusted using the false discovery rate (FDR) method for multiple comparisons.

Furthermore, given that given that a large portion of the PLHIV cohort (48.0%) was not virally suppressed, we conducted a sub-analysis including only PLHIV with undetectable plasma HIV RNA (n=345). Finally, given that the CAN− group showed a broader age range distribution (ages 18-79) compared to CAN+ group (ages 18-65), we conducted a sub-analysis excluding individuals ages 65 and up, resulting in a restricted sample (n=923). All covariates from whole sample models were included in the sub-analysis models.

Results

Study Cohort.

Participants ranged in age from 18 to 79 years old (*M*=43.2, SD=11.7), and were predominantly men 76.4%. The majority of men identified as gay or bisexual (70.7%), while the majority of women identified as heterosexual (93.8%). In terms of race/ethnicity, the cohort was 49.8% White, 26.7% Black or African American, 17.3% Hispanic or Latino, and 6.2% Other. Sample characteristics including demographic, psychiatric, substance use, and HIV disease and treatment variables by HIV/CAN group are presented in Table 2.

Cannabis Characteristics.

15.8% (n=150) of the study sample fell into our CAN+ group. In terms of CAN+ older adults, there were 13 CAN+ PLHIV and 22 CAN+ HIV− individuals ≥ 50 years old and no CAN+ individuals in either HIV status group who were > 65 years old. Cannabis use characteristics within the CAN+ group are presented in Table 3. The average age of first use was 15.6 years old (*SD*=5.0), average lifetime grams per day was 1.3 (*SD*=1.8) (*Median*=0.6, *IQR*=0.3, 1.5) and median days since last use was 5 (*IQR*=1, 60.9). For CAN+ group, the median total lifetime estimated grams of use was 1724 grams (*IQR*=454, 5542), and total lifetime estimated days of use was 2670 (*IQR*=1105, 5297). For CAN− group, only 349 participants reported cannabis use (the remaining n=453 reported no use or less than five uses in their lifetime), and in this subgroup, the median total lifetime estimated grams of use was 7.5 grams (*IQR* = 1, 93), and total lifetime estimated days of use was 53 (*IQR* = 6, 470). For CAN− individuals with prior cannabis exposure, their cannabis use was highly remote, with an average of 13.9 years since last use.

Cannabis exposure tended to be higher in younger adults (< age 50) compared to older adults (≥age 50), but this was not statistically significant (p=0.08). Cannabis exposure did not differ by HIV status groups (p=0.85), but was higher in men compared to women

(p<0.001), and in Whites and African Americans compared to Latinos (p<0.002, p<0.02, respectively). In terms of sexual orientation, bisexual individuals (n=81, 91.7% men) had higher cannabis exposure compared to heterosexual and gay individuals, but this difference was not statistically significant (p=0.06).

NCI across HIV and Cannabis groups.

Rates of NCI differed significantly across HIV/CAN groups (Chi square=44.1, df=3, p<0.001) (Figure 1). In analyses unadjusted for covariates, among PLHIV (n=679), NCI rates were lower for those with cannabis exposure (Chi square=14.3, df=1, p<0.001). Conversely, among HIV− individuals (n=273), NCI did not differ by cannabis exposure (Chi square=0.04, df=1, p=0.84). In analyses with the PLHIV sample restricted to those with undetectable plasma HIV RNA viral load (n=345), findings did not differ from the whole sample analyses.

Cannabis, HIV, and Age on NCI.

Table 4 presents our multivariable logistic regression analysis findings predicting NCI. Controlling for race/ethnicity, current MDD, and past methamphetamine use disorder, the three-way age X HIV X cannabis interaction was not significant (p=0.17) (Table 4, Model 1a), and thus we removed it from our model. With only the lower-order two-way interactions included, a significant cannabis X HIV interaction was detected (p=0.045), while the age X cannabis interaction (p=0.10), and the age X HIV interaction (p=0.93) were not significant (Table 4, Model 1b). When we removed the non-significant age interactions from our model, the cannabis X HIV interaction remained significant (p=0.02) (Table 4, Model 1c). Probing the cannabis X HIV interaction revealed that cannabis exposure was associated with lower odds of NCI among PLHIV (OR=0.53, 95% CI=0.33–0.85, p=0.009), and was not related to NCI among HIV− individuals (OR=1.41, 95% CI=0.63–3.16, p=0.40) (Table 4, Models 2a, 2b; Figure 2). In analyses with the undetectable PLHIV sample and separately, in the age restricted sample (ages ≤65), controlling for the same covariates, findings in both sub-samples showed a similar pattern to the whole sample analyses.

Cannabis on Cognitive Domains by HIV Status.

Given cannabis exposure was related to lower odds of NCI among only PLHIV, we stratified groups by HIV status. Among PLHIV with relevant covariates and FDR adjusted *p* values, cannabis exposure was associated with higher performance in verbal fluency (p=0.02, coefficient = 2.86) and learning (p=0.02, coefficient = 2.70) domains, while among HIV− individuals, cannabis exposure was not significantly associated with any of the seven cognitive domains.

Discussion

Our findings present evidence that cannabis exposure was associated with lower odds of NCI in the context of HIV, while cannabis exposure showed no relation to NCI among HIV− individuals, consistent with our first hypothesis. We did not detect age as a moderating factor of cannabis nor HIV disease on NCI. While cannabis exposure was associated with a lower proportion of NCI among PLHIV regardless of age, the magnitude of the association was

not greater among older PLHIV compared to younger PLHIV, contrary to our second hypothesis. Our findings did not differ when the sample was restricted to undetectable PLHIV nor, separately, when the sample was restricted to ages 18-65. When cognitive performance was assessed by domain, cannabis exposure was associated with higher verbal fluency and learning performance only among PLHIV.

To our knowledge, this is the first study to show that cannabis use was related to a lower odds of global neurocognitive impairment and better verbal and learning performance in the context of HIV disease in a large and racially/ethnically diverse cohort. Our results differ from previous work that has shown primarily null or adverse effects of cannabis on cognition in PLHIV[27,45,46] with adverse findings found selectively among frequent cannabis users (daily use, moderate-to-heavy users: 3+ times per day), and on specific cognitive domains (delayed recall, learning); further, the adverse effects of cannabis on cognition identified by Cristiani and colleagues (2004) were limited to PLHIV with symptomatic HIV disease. Chang and colleagues (2006) observed no interactive effects between HIV disease and cannabis use (>4 days per week) on any neurocognitive test. Thames and colleagues (2016) found global neurocognitive performance was similar among PLHIV and HIV− individuals who were light cannabis users (light users: at least weekly use, less than 2 times per day), and PLHIV light users showed better performance in verbal fluency compared to HIV− light users. The association between cannabis exposure and higher performance in verbal fluency in PLHIV is supported by the current study's findings. A clear methodological issue in the field of cannabis-cognition research is differences in how cannabis exposure is defined, which may explain for some of the variation in outcomes. Given the small and mixed state of the literature, this study provides an important insight into the complex relationship of cannabis exposure and neurocognitive functioning in HIV.

Our results are consistent with the idea that under some circumstances cannabis might be neuroprotective. If correct, possible mechanisms may involve the endocannabinoid modulatory effects of cannabis, which may mitigate some forms of neural injury in HIV disease. Studies of human and mouse cannabinoid systems in the context of neuroinflammatory exposures show that cannabinoid 2 receptors (CB_2) are highly upregulated during inflammatory insult and selective activation of CB_2 receptors reduces blood brain barrier (BBB) dysfunction[24], vascular inflammation and pathological microglial activation, thus indirectly decreasing oxidative stress and subsequent cell death[47], and HIV-associated synapse loss[48]. Taken together, this literature cumulatively suggests there may be some therapeutic potential of compounds that target the cannabinoid system through modulation of neurotoxic and inflammatory processes in HIV disease and other neuroinflammatory diseases[49,50]. Given our findings did not differ in virally suppressed PLHIV, the anti-inflammatory effects of cannabis may be important for PLHIV who are both detectable and undetectable. For undetectable PLHIV, magnetic resonance spectroscopy (MRS) biomarkers suggest that neuroinflammation and lower neuronal integrity persist despite virologic suppression on cART[51].

Still, future research must further elucidate what levels of cannabis exposure are associated with optimal brain and neurocognitive health. For example, we are aware of at least one neuroimaging study specifically focusing on combined effects of cannabis exposure and

HIV[26]. This study found that higher levels of cannabis exposure related to smaller entorhinal cortex and fusiform gyrus volumes, regardless of HIV status. Although further neuroimaging studies are needed to support conclusions, integrated findings from this study and those previously mentioned in this report suggest that cannabis exposure may only have beneficial effects on brain health up to a certain level of use, beyond which effects may be detrimental.

Next, given the lack of age effects observed in our analyses, one interpretation of our findings is that the effects of cannabis are protective for PLHIV across the age spectrum. However, it is also possible that our study was underpowered to detect an age X cannabis interaction due to the small sample size of older adults with cannabis exposure. Given these small numbers of older adults, the lack of differences in rates of cannabis use between younger and older adults in our study, and the trend-level age X cannabis interaction, the lack of age effects detected on rates of NCI should be interpreted with caution. As therapeutic and recreational use of cannabis compounds increases among older adults, future research examining these relationships specifically in larger samples of older adults (ages 60+) is warranted.

Study strengths include a large sample size of community-dwelling PLHIV and HIV− individuals. While the racial/ethnic demographics of our cohort do not match the national PLHIV population (42% Black/African American, 23% Latino/Hispanic, 30% White, 5% Other)[52], our PLHIV cohort does include substantial representation of Black/African American (n=207, 30.5%) and Latino/Hispanic (n=123, 18.1%) PLHIV, who are disproportionately affected by HIV in the U.S. Additionally, our study employed a comprehensive neuropsychological battery to assess cognitive functioning and used multiple tests to tap seven domains of cognition, compared to previous studies which used brief cognitive batteries. Furthermore, our analyses controlled for more predictors of neurocognitive outcomes in PLHIV than previous studies, and our results remained significant even after controlling for covariates such as past history of methamphetamine use disorder and current MDD, revealing a unique and robust contribution of cannabis exposure to neurocognitive outcomes in PLHIV. It is also of interest that the PLHIV/CAN+ group performed better neurocognitively despite having other risks that might have predicted the opposite (e.g., greater frequency of past alcohol and cocaine use disorder).

These analyses are not without their limitations. Cross-sectional design precludes detection of casual effects from the observed associations between cannabis, HIV disease, and neurocognitive impairment. Longitudinal studies are necessary to determine the direction of effects between these exposures and outcomes. While epidemiological studies show higher rates of cannabis use among PLHIV compared to the general population, our PLHIV and HIV− control group showed similar rates of cannabis exposure (current year cannabis use and past cannabis use disorder). This discrepancy with the literature is likely attributable to our research center’s recruitment of HIV− individuals with similar levels of exposure to comorbid conditions (such as substance use and psychiatric disorders) as observed in our PLHIV cohort, to provide an appropriate comparison group. Correspondingly, our HIV− cohort is not intended to be representative of the general population. This method of recruitment for our HIV− cohort may also explain the overall high rates of NCI observed in even the HIV−/CAN− group, as this group presents with higher levels of socioenvironmental

exposures and conditions linked to NCI compared to the general population. In order to limit the influence of substances besides cannabis on our findings, we excluded recent non-cannabis substance use disorders in the past year; however, as poly substance use is highly prevalent in our population, we considered as covariates rather than exclude for past lifetime history to increase the generalizability of our findings. A large proportion of the PLHIV cohort were not virally suppressed, which is partially attributable to lower rates of ART use, earlier ART regimes which were less potent and less well tolerated, and distinguishes this cohort from some other contemporary research HIV cohorts. In order to ensure that our study findings did not differ by detectable status, we conducted a sub-analysis in the virally suppressed PLHIV cohort that showed a similar pattern of results. In terms of the generalizability of our PLHIV cohort, national epidemiological data shows that only approximately 50% of PLHIV in the U.S. are virally suppressed, due to disparities in the HIV care continuum[53]. Thus, the current study's rate of PLHIV with detectable plasma HIV RNA is generally representative of the U.S.'s PLHIV population. Additionally, this study utilized retrospective self-report of cannabis use, which is vulnerable to inaccurate reporting, especially when reporting cannabis use from the remote past via our modified lifetime TLFB interview. We were also limited by using a categorical approach which captured problematic use via cannabis use disorder diagnosis, and lacked detailed characterization of cannabis exposure.

Future investigations that capture the continuous and multi-dimensional spectrum of cannabis use, including the effects of dose, timing/frequency of use, and potency/composition of cannabis product [e.g. Δ 9-tetrahydrocannabinol (THC) vs. cannabidiol (CBD) content], are needed to define a potential optimal neuroprotective range of cannabis use, as well as, define parameters of use that are neutral or harmful to neurocognition. Assessing contextual factors of cannabis use is critical to capturing the complexity of life conditions of individuals who use cannabis products and/or live with HIV and have been left unmeasured in many studies of cannabis use and neurocognition: psychosocial and socioeconomic context, motivations for cannabis use, and exposure to other substances and diseases. Future work from this research group aims to assess and investigate these factors. While our study did not observe age modulating the relationship of cannabis use and neurocognition, older adults (ages 60+) represent an important and understudied group in the literature on the non-acute effects of cannabis on neurocognition, with few studies that show some null and mixed cannabis effects on cognitive domains in older adults[54]. To further probe the findings of the current study, investigation of mechanisms underlying potential neuroprotective effects of cannabis is of major interest via BBB function, neuroimmune and neuroinflammatory processes, and gut microbiome signaling. The current study expands the available cannabis-neurocognition literature, suggests a link between cannabis exposure and a lower likelihood of neurocognitive impairment, and signals considerable future work is needed to clarify the parameters of cannabis' possible neuroprotective effects in brain structure/function and neurocognition among PLHIV across the lifespan.

Acknowledgments

This work was supported by the National Institute of Health (NIH) and the National Institute of Mental Health (NIMH): 1) The CNS HIV Anti- Retroviral Therapy Effects Research (CHARTER) study is supported by awards

N01MH22005, HHSN271201000036C, and HHSN271201000030C from NIH; 2) the HIV Neurobehavioral Research Center (HNRC) is supported by Center award P30MH062512 from NIMH; 3) the California NeuroAIDS Tissue Network (CNTN) is supported by awards U01MH083506, R24MH59745, and U24MH100928 from NIMH; 4) the Translational Methamphetamine AIDS Research Center (TMARC) is supported by award P50DA026306 from NIDA; 5) NeuroAIDS: Effects of Methamphetamine is supported by P01DA12065 from NIDA. CWW was supported by NIDA award T32-DA031098. EWP was supported by NIAAA award F31-AA027198. EES was supported by Interdisciplinary Research Fellowship in NeuroAIDS award R25MH081482 and Sustained Training in HIV and Aging (STAHR) Training Grant R25 MH108389.

Conflicts of Interest and Source of Funding: This work was supported by the National Institute of Health (NIH) and the National Institute of Mental Health (NIMH): 1) The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study is supported by awards N01MH22005, HHSN271201000036C, and HHSN271201000030C from NIH; 2) the HIV Neurobehavioral Research Center (HNRC) is supported by Center award P30MH062512 from NIMH; 3) the California NeuroAIDS Tissue Network (CNTN) is supported by awards U01MH083506, R24MH59745, and U24MH100928 from NIMH; 4) the Translational Methamphetamine AIDS Research Center (TMARC) is supported by award P50DA026306 from NIDA; 5) NeuroAIDS: Effects of Methamphetamine is supported by P01DA12065 from NIDA. CWW was supported by NIDA award T32-DA031098. EWP was supported by NIAAA award F31-AA027198. EES was supported by Interdisciplinary Research Fellowship in NeuroAIDS award R25MH081482 and Sustained Training in HIV and Aging (STAHR) Training Grant R25 MH108389. The authors declare no conflicts of interest.

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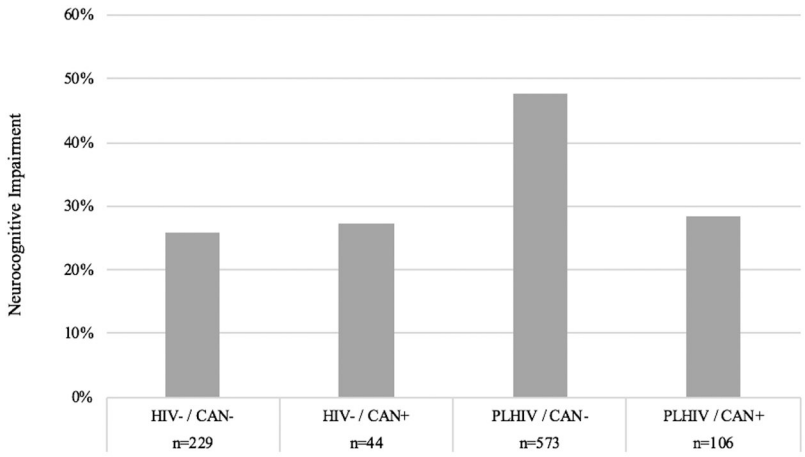

Figure 1.

Neurocognitive Impairment by HIV Status and Cannabis Exposure

Note: HIV−, People Living without HIV; PLHIV, People Living with HIV; CAN+, cannabis exposure group; CAN−, non-cannabis exposure group

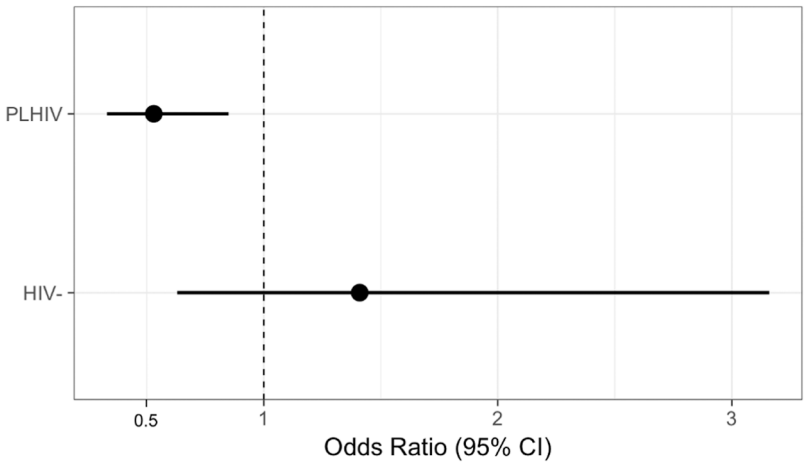

Figure 2.

Forest Plot showing Odds Ratios of Cannabis Exposure for Neurocognitive Impairment in PLHIV and HIV− individuals

Note: HIV−, People Living without HIV; PLHIV, People Living with HIV; CAN+, cannabis exposure group; CAN−, non-cannabis exposure group

Table 1.

Neurocognitive battery: Individual tests comprising each neurocognitive domain

Neurocognitive Domain	Individual Measures
Verbal fluency	Controlled Oral Word Association Test Category Fluency (Animals) Category Fluency (Actions)
Executive function	Wisconsin Card Sorting Test (64-item) Trail Making Test, Part B Stroop Color Word Trial
Processing speed	WAIS-III Digit Symbol WAIS-III Symbol Search Trail Making Test, Part A Stroop Color Trial
Learning	Learning Trials of: Hopkins Verbal Learning Test-Revised Brief Visuospatial Memory Test-Revised
Delayed recall	Delayed Recall Trials of: Hopkins Verbal Learning Test-Revised Brief Visuospatial Memory Test-Revised
Working memory	WAIS-III Letter-Number Sequencing PASAT (1st channel only)
Motor skills	Grooved Pegboard Test (dominant & non-dominant hands)

Notes: WAIS III, Wecshler Adult Intelligence Scale 3rd Edition; PASAT, Paced Auditory Serial Addition Task

Table 2.

Cohort characteristics (N=952), Mean(SD), Median [IQR], or %

	HIV− / CAN − [1], n=229	HIV− / CAN+ [2], n=44	PLHIV / CAN − [3], n=573	PLHIV / CAN+ [4], n=106	Group diff. (p-value)	Group differences Pairwise comparisons	Association with NCI (p-value)
Demographics							
Age	43.4 (14.7)	37.8 (13.3)	43.7 (10.6)	42.4 (8.9)	0.01	[1],[3] > [2]	<.001
Years of Education	13.8 (2.4)	13.1 (2.6)	13.4 (2.8)	13.0 (2.3)	0.03	[1] > [4]	0.10
Sex/Gender (% Women)	39.7%	20.5%	20.4%	7.5%	<.001	[1] > [2],[3]>[4]	0.32
Ethnicity/race					<.001		0.05
White	57.2%	61.4%	44.9%	55.7%			
Black/African American	16.2%	22.7%	30.5%	30.2%		[3] > [1][a]	
Latino/Hispanic	17.0%	6.8%	19.6%	10.4%			
Other	9.6%	9.1%	5.1%	3.8%			
Sexual Orientation (% gay or bisexual)	22.5%	27.3%	67.0%	75.5%	<.001	[3],[4] > [1],[2]	0.38
Psychiatric							
Current MDD	3.5%	6.8%	13.1%	14.2%	<.001	[3],[4] > [1]	0.005
Lifetime MDD	25.3%	29.6%	43.6%	58.5%	<.001	[4] > [3] > [1],[2]	0.34
Substance Use							
Past Alcohol Use Disorder	21.8%	68.2%	32.6%	67.9%	<.001	[2],[4] > [3] > [1]	0.24
Past Cocaine Use Disorder	3.9%	22.7%	10.3%	41.5%	<.001	[4] > [2],[3] > [1]	0.83
Past Meth Use Disorder	8.7%	34.1%	8.9%	35.9%	<.001	[2],[4] > [1],[3]	0.003
Past Opioid Use Disorder	3.5%	18.2%	3.5%	9.4%	<.001	[2] > [1],[3]	0.79
Past Sedative Use Disorder	0.4%	9.1%	1.1%	15.1%	<.001	[2],[4] > [1],[3]	0.80
Disease							
Hepatitis C	17.0%	25.0%	17.3%	16.0%	0.62		0.07
AIDS status (% AIDS)	-	-	58.1%	58.5%	0.94		<.001
Duration of HIV disease (years)	-	-	9.3 (7.0)	9.0 (6.9)	0.62		0.10
cART status (% on)	-	-	71.5%	75.0%	0.46		0.01
Nadir $CD4^+$ T cell count,	-	-	190 [50, 300]	184 [40, 323]	0.50		<.001
Current $CD4^+$ T cell count,	-	-	442 [268, 643]	475 [303, 665]	0.95		0.34
Plasma viral load (% detectable)	-	-	48.3%	46.2%	0.36		0.21

	HIV− / CAN − [1], n=229	HIV− / CAN+ [2], n=44	PLHIV / CAN − [3], n=573	PLHIV / CAN+ [4], n=106	Group diff. (p-value)	Group differences Pairwise comparisons	Association with NCI (p-value)
CSF viral load (% detectable)[b]	-	-	28.3%	26.9%	0.81		0.91

Notes: HIV−, People Living without HIV; PLHIV, People Living with HIV; CAN+, cannabis exposure group; CAN−, non-cannabis exposure group; MDD, Major Depressive Disorder; AIDS, acquired immune deficiency syndrome; cART, combination antiretroviral therapy; IQR, interquartile range

Pairwise comparisons: [a]Proportion of people of color (Black, Latino, and Other) to White; Missing Values: [b]data present for n=506

Table 3.

Cannabis Use Characteristics of CAN+ group (n=150), Mean(SD) or Median(IQR)

	Overall cohort	HIV− n=44	PLHIV n=106	p-value
Age of First Use	15.6 (5.0)	15.1 (4.7)	15.8 (5.1)	0.41
Average lifetime grams/day	1.3 (1.8)	1.2 (1.7)	1.4 (1.8)	0.58
Days Since Last Use	5 (1, 60.9)	10 (2, 109)	3 (1, 42)	0.09

Note: CAN+, cannabis exposure group; HIV−, People Living without HIV; PLHIV, People Living with HIV; IQR, interquartile range

Table 4.

Cannabis Exposure is Associated with Lower Probability of Neurocognitive Impairment in PLHIV

Model 1a: Neurocognitive Impairment		
n=952		
Variable	**Odds Ratio (95% CI)**	**p-value**
Age	1.03 (1.01-1.05)	0.007
HIV+ (vs. -)	2.62 (1.84-3.75)	<.001
CAN+ (vs. -)	1.07 (0.45-2.52)	0.87
Age*HIV	--	0.69
Age*CAN	--	0.10
HIV*CAN	--	0.14
Age*HIV*CAN	--	0.17

Model 1b: Neurocognitive Impairment		
n=952		
Variable	**Odds Ratio (95% CI)**	**p-value**
Age	1.03 (1.01-1.05)	0.02
HIV+ (vs. -)	2.59 (1.82-3.69)	<.001
CAN+ (vs. -)	1.25 (0.57-2.72)	0.57
Age*HIV	--	0.93
Age*CAN	--	0.10
HIV*CAN	--	0.045

Model 1c: Neurocognitive Impairment		
n=952		
Variable	**Odds Ratio (95% CI)**	**p-value**
Age	1.02 (1.01-1.03)	<.001
HIV+ (vs. -)	2.58 (1.82-3.66)	<.001
CAN+ (vs. -)	1.43 (0.67-3.02)	0.35
HIV*CAN	--	0.02

Model 2a: Neurocognitive Impairment		
Stratified in HIV−		
n=273		
Variable	**Odds Ratio (95% CI)**	**p-value**
CAN+ (vs. -)	1.41 (0.63-3.16)	0.41

Model 2b: Neurocognitive Impairment		
Stratified in PLHIV		
n=679		
Variable	**Odds Ratio (95% CI)**	**p-value**
CAN+ (vs. -)	0.53 (0.33-0.85)	0.009

Note: All models (1a,1b, 1c, 2a, 2b) are adjusted for covariates: ethnicity/race, current major depressive disorder and past methamphetamine use disorder; In Models 1abc, the conditional effect of HIV disease is within the non-cannabis exposure reference group, and the conditional effect of cannabis exposure is within the HIV− reference group; HIV −, People Living without HIV; PLHIV, People Living with HIV; CAN+, cannabis exposure group; CAN−, non-cannabis exposure group