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Objective: Many people with HIV (PWH) are at risk for age-related neurodegenerative disorders such as Alzheimer's disease (AD). Studies on the association between cognition, neuroimaging outcomes, and the Apolipoprotein E4 (APOE4) genotype, which is associated with greater risk of AD, have yielded mixed results in PWH; however, many of these studies have examined a wide age range of PWH and have not examined *APOE* by race interactions that are observed in HIV-negative older adults. Thus, we examined how *APOE* status relates to cognition and medial temporal lobe (MTL) structures (implicated in AD pathogenesis) in mid- to older-aged PWH. In exploratory analyses, we also examined race (African American (AA)/Black and non-Hispanic (NH) White) by *APOE* status interactions on cognition and MTL structures.
Participants and Methods: The analysis included 88 PWH between the ages of 45 and 68 (mean age=51±5.9 years; 86% male; 51% AA/Black, 38% NH-White, 9% Hispanic/Latinx, 2% other) from the CNS HIV Antiretroviral Therapy Effects Research multi-site study. Participants underwent *APOE* genotyping, neuropsychological testing, and structural MRI; *APOE* groups were defined as APOE4+ (at least one APOE4 allele) and APOE4- (no APOE4 alleles). Eighty-nine percent of participants were on antiretroviral therapy, 74% had undetectable plasma HIV RNA (<50 copies/ml), and 25% were APOE4+ (32% AA/Black/15% NH-White). Neuropsychological testing assessed seven domains, and demographically-corrected T-scores were calculated. FreeSurfer 7.1.1 was used to measure MTL structures (hippocampal volume, entorhinal cortex thickness, and parahippocampal thickness) and the effect of scanner was regressed out prior to analyses. Multivariable linear regressions tested the association between *APOE* status and cognitive and imaging outcomes. Models examining cognition covaried for comorbid conditions and HIV disease characteristics related to global cognition (i.e., AIDS status, lifetime methamphetamine use disorder). Models examining the MTL covaried for age, sex, and relevant imaging covariates (i.e., intracranial volume or mean cortical thickness).
Results: APOE4+ carriers had worse learning (β=-0.27, *p*=.01) and delayed recall (β=-0.25, *p*=.02) compared to the APOE4- group, but *APOE* status was not significantly associated with any other domain (*p*s>0.24). APOE4+ status was also associated with thinner entorhinal cortex (β=-0.24, *p*=.02). *APOE* status was not significantly associated with hippocampal volume (β=-0.08, *p*=0.32) or parahippocampal thickness (β=-0.18, *p*=.08). Lastly, race interacted with *APOE* status such that the negative association between APOE4+ status and cognition was stronger in NH-White PWH as compared to AA/Black PWH in learning, delayed recall, and verbal fluency (*p*s<0.05). There were no *APOE* by race interactions for any MTL structures (*p*s>0.10).
Conclusions: Findings suggest that APOE4 carrier status is associated with worse episodic memory and thinner entorhinal cortex in mid- to older-aged PWH. While APOE4+ groups were small, we found that APOE4 carrier status had a larger association with cognition in NH-White PWH as compared to AA/Black PWH, consistent with studies demonstrating an attenuated effect of APOE4 in older AA/Black HIV-negative older adults. These findings further highlight the importance of recruiting diverse samples and suggest exploring other genetic markers (e.g., *ABCA7*) that may be more predictive of AD in some races to better understand AD risk in diverse groups of PWH.

Categories: Infectious Disease (HIV/COVID/Hepatitis/Viruses)
Keyword 1: genetics
Keyword 2: memory disorders
Keyword 3: neuroimaging: structural
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4 HIV Status and Cannabis Use: A Rigorous Examination of Between Group Differences in Neurocognitive Functioning

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Objective: A recent review called for a more robust assessment of cannabis use (CU), including amount and timing of recent use to assess neurocognitive effects of CU among people living with HIV (PWH) (Ellis et al., 2021). The current study addresses some issues raised by investigating between group neurocognitive differences among healthy controls and PWH who differ on their cannabis use histories, using strict inclusion criteria, robust classification of CU, and administration of an established neurocognitive test battery.
Participants and Methods: Among this community sample of adults (N=309), 58 were classified as CU+/HIV+ group (84.5% Male), 76 as CU-/HIV+ (57.9% M), 86 as CU+/HIV- (58.1% M), and 89 as CU-/HIV- (53.9% M). Exclusion criteria included history of past 12-month dependence and extensive lifetime dependence or significant use of illicit substances other than cannabis, severe or current mood or thought disorder, and other medical conditions that adversely impact neurocognitive functioning. Inclusion criteria for CU+ groups included <30-days since last CU, >10 times of CU in last month, 3 times of CU per month in last 12 months, > 1 year of CU, and > 500 times used in lifetime. CU parameters did not statistically differ between HIV+/CU+ and HIV-/CU+. CU- groups' inclusion criteria required no CU in last 6 months, 196 lifetime number of times used, and no history of CU dependance. Lifetime CU did not statistically differ between CU-/HIV+ and CU-/HIV- groups. HIV+ groups did not differ significantly on HIV viral load in plasma or nadir CD4+ counts. Significant between group differences included age, sex, years of education, and amount of alcohol and nicotine use within 12 months. The aforementioned sociodemographic and substance use variables that differed between groups were covariates in analyses. A battery of 10 neurocognitive measures, two measures per each domain of learning, memory, motor, executive functioning, and processing speed. Global composite summary scores for overall neurocognitive performance were calculated by averaging M T-scores for each neurocognitive domain. Data transformations were used to address any violations of statistical assumptions.
Results: To facilitate data reduction, neurocognitive task scores were standardized to T-scores using the M and SD of the CU-/HIV- group. An omnibus model of between-group comparisons on global neurocognitive task performance revealed no significant differences, $F(3) = .16$, $p = .923$. Subsequent Tukey's post hoc test revealed no significant differences among the four groups. Results also revealed nonsignificant differences between groups in neurocognitive performance within each domain. However, the CU-/HIV- group performed significantly worse than the CU-/HIV+ group on the Executive Functioning domain, based on Tukey's post hoc test.
Conclusions: We found no significant global neurocognitive differences among groups; however, there was some evidence for domain-specific neurocognitive differences in executive functioning. This contrasts somewhat with existing literature on HIV and cannabis-associated neurocognitive deficits. Several factors may have contributed to this, including our relatively healthy PWH sample. Future analyses will examine interactive effects of HIV severity and severity of CU on neurocognition. This analysis will better determine who, among PWH, are most at-risk for cannabis-associated neurocognitive effects and what factors may exacerbate them.

Categories: Infectious Disease (HIV/COVID/Hepatitis/Viruses)
Keyword 1: neurocognition
Keyword 2: HIV/AIDS
Keyword 3: substance abuse
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5 The Association of Neighborhood Socioeconomic Deprivation with Neurocognition in a Diverse Cohort of Middle- and Older-Aged Persons Living with and Without HIV

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