

Effects of *APOE*- ϵ 4, Age and HIV on Glial Metabolite and Cognitive Deficits

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INTRODUCTION: Despite effective plasma viral suppression with antiretroviral medications, milder forms of HIV-associated neurocognitive disorders (HAND) remain prevalent.¹ The diagnosis of HAND is often difficult in the clinical setting; better predictive biomarker is needed. The well known Alzheimer risk allele, apolipoprotein-E(*APOE*)- ϵ 4, was inconsistently found to increase the risk for HAND.²⁻⁵ However, the antagonistic pleiotropy effect of *APOE*- ϵ 4 (the gene is expressed differently in young vs. old ages) was found only in HIV-seronegative- ϵ 4 subjects, while HIV+ ϵ 4 subjects already showed greater brain atrophy at younger age.⁶ Whether HIV subjects with *APOE*- ϵ 4 allele(s) would show greater neuroinflammation, which may contribute to cognitive deficits, across the ages is unknown and was evaluated.

METHODS: 177 participants, 75% of White or mixed race [97 seronegative (SN) subjects: ages 44.7 \pm 1.3 years, 85 (87.6%) men, 28(28.9%) *APOE* ϵ 4+; 80 HIV-infected subjects: ages 47.3 \pm 1.1 years, 73(91.3%) men, 23(28.8%) *APOE* ϵ 4+] fulfilling study criteria were scanned using a 3 Tesla MR scanner (Tim Trio, Siemens Medical Solutions, Erlangen, Germany). ¹H MRS was performed in four brain regions, using the PRESS sequence (TR/TE=3000/64 ms, 64 NEX), and T2 decay of water at 10 echo times to correct for partial volumes of CSF in each voxel. MRS data were processed using a customized version of the spectral analysis package of LCModel⁷ to determine concentrations of major brain metabolites (NAA, Cho, tCr, GLX and MI) in each voxel. Each participant was also assessed with a battery of neuropsychological tests that included the 7 cognitive domains required to assess for the presence of HAND.

RESULTS: Clinical: The SN and HIV subjects were similar in age, sex proportion (82-90% male), years of education, the proportion of *APOE* ϵ 4+ carriers. The two groups also had similar distributions of race and ethnicity, predominantly white (52-64% per group) or mixed race (14-22%) individuals and very few Blacks (0-7%). The two HIV+ groups (*APOE* ϵ 4- versus *APOE* ϵ 4+) were not different in their CD4 counts, nadir CD4 count, Log viral load, Karnofsky score, HIV dementia scale and duration of HIV diagnosis. However, both HIV groups had more depressive symptoms on the Center for Epidemiological Scale-Depression (CES-D) than the two SN groups. All *APOE* ϵ 4+ subjects, regardless of HIV status, performed worse than *APOE* ϵ 4- subjects ($p=0.04$) on the Attention/Working Memory domain, and only HIV but not SN subjects with *APOE* ϵ 4+ status performed worse than SN *APOE* ϵ 4- subjects on executive function and verbal fluency.

¹HMRS (see Figure 1): Compared to SN controls, HIV- subjects with or without *APOE*- ϵ 4, showed higher levels of *myo*-inositol in frontal white matter across the ages, without the antagonistic pleiotropy effects seen in SN- ϵ 4+ subjects. However, elevated *myo*-inositol in the parietal cortex was also found only in seronegative- ϵ 4+ subjects. In contrast, all ϵ 4+ subjects had lower total creatine levels in their basal ganglia. On neuropsychological tests, while all infected subjects showed poorer attention and working memory, ϵ 4+infected subjects additionally showed poorer fluency, memory and executive function. The higher levels of *myo*-inositol were associated with poorer cognitive performance.

DISCUSSION: This the first study to show the interactive effects of *APOE*- ϵ 4 and HIV infection on brain metabolites. HIV+ individuals with *APOE*- ϵ 4 had the poorest cognitive performance. However, having HIV appears to ameliorate the antagonistic pleiotropy effect of ϵ 4+ since *myo*-inositol was prematurely elevated in the younger infected subjects, which in turn contributed to the cognitive deficits in all HIV subjects with the *APOE*- ϵ 4. Therefore, the *APOE*- ϵ 4 may be a useful clinical biomarker to identify White and mixed raced HIV-infected individuals who are at risk for HAND.

ACKNOWLEDGMENTS: NIH grant support (2K24DA16170; 2R01MH61427; U54NS/DA56883). We also thank our research participants, as well as the many technical and clinical staff at the Neuroscience and MR Research Program at the JABSOM for assistance with data collection.

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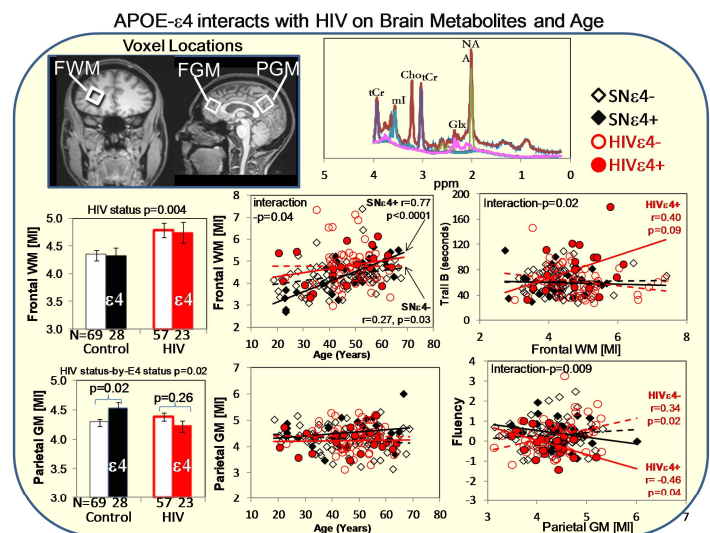


Figure 1. Top figure: Voxel locations and representative MR spectra. **Bottom charts:** Data from 97 SN controls and 80 HAART-stable HIV. Higher myo-inositol only in frontal WM of HIV (red bars) compared to SN controls (black and white bars). Abnormal levels of myo-inositol associated with poorer cognitive performance only in HIV subjects with *APOE*- ϵ 4 allele(s).