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Neuroinflammation and Reactive Gliosis During Long Term ART Initiated in Acute HIV

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Background:

- HIV has been identified in cerebrospinal fluid (CSF) as early as 14 days after infection (1). Numerous HIV laboratory and neuroimaging studies confirmed central nervous system immune activation and inflammation in acute and chronic HIV (for review see (3)).
- We previously revealed neuroimaging biomarkers of inflammation during untreated acute HIV infection (AHI) (1,2). To date, no studies have examined these neuroimaging biomarkers before and after sustained use of suppressive cART. We addressed this knowledge gap using high resolution proton MRS acquired prospectively in AHI participants enrolled in RV254/SEARCH 010.

Methods

- Participants included Thai male AHI (n=109) and a comparison sample of demographically similar HIV–uninfected controls (HC; n=21).
- Single voxel proton brain MRS was acquired on a 3T Phillips MR scanner using standard single voxel double spin echo data acquisition with an echo time (TE) of 35ms. Metabolites were measured in basal ganglia (BG) and the left frontal white matter (WM).
- MRS was acquired before cART (month 0; M0) and again at month 6 (M6; n=42) and month 24 (M24; n=62) of suppressive cART. A subset of individuals underwent MRS at month 60 (M60; n=25). Additionally, 31 individuals completed neuropsychological testing (NPZ-4) at M0 and M24.

Data processing and statistical analysis:

- LCModel (version 6.3.1j) was used to quantify brain metabolites using GAMMA simulated reference basis sets.

Study Summary:

- MRS confirms persistent neuroinflammation 24 months after cART initiated during AHI.
- Glial cell proliferation (reactive gliosis) increased from baseline (pre-cART) to month 24 follow-up.

- The LCModel outputs were corrected for T1, T2 relaxation times as well as gray matter, white matter, and CSF contribution within the MRS voxel of interests.
- Non-parametric Mann-Whitney and Wilcoxon test were used for comparisons.

Results:

- All 109 participants were male.
- At baseline, median age (27 yrs; range = 18-65), estimated duration of infection (19 days; range = 3-49), CD4 count (343; range =101-1302 cells/mm), and plasma HIV RNA=6.06 (log, copies/mL). Median CD4 count, plasma HIV RNA, and NPZ-4 improved significantly with cART.
- In **BG**, total choline (tCho/tCr) and glutamate (Glu/tCr) were elevated at M0 compared to HC ($p < 0.0001$) and decreased to normative levels after an average of 60 months of cART (Figure 1a).
- Within the subset of 31 individuals with NPZ data, tCho/tCr was elevated at M0 ($p= 0.0002$) and remained elevated after 24 months of cART ($p=0.048$) compared to HC (Figure 1b).

Baseline levels of **WM** myo-inositol (Ins/tCr) were similar between groups, but differed at M24, with higher levels observed among AHI ($p<0.0001$), Figure 1b).

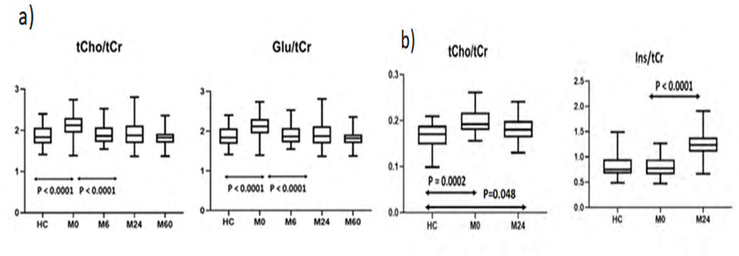


Figure 1a: **BG**: tCho/tCr and Glu/tCr between HIV at M0, M6, M24, and M60 and HC. 1b: From the 31 subset; **BG**: tCho/tCr and **WM** Ins/tCr between HIV at M0 and M24 and HC.

Conclusions:

This high field (3T) MRS study reveals distinct signatures of neuroinflammation in treatment naïve AHI (increased tCho and Glu) and after 24 months of cART (increased tCho and Ins). The development of increased Ins after cART suggests the development of reactive gliosis (3) despite early cART.

References:

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Disclaimers:

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