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Cerebral Glutathione Metabolism in Acute HIV Infection and Response to ART

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Background

- Glutathione (GSH) is the major brain antioxidant.
- HIV infection is associated with generation of reactive oxygen and nitrogen species (ROS/NOS).
- Imbalance between ROS/NOS and the brain antioxidants can result in oxidative stress damaging DNA, lipid peroxidation and protein oxidation.

Methods

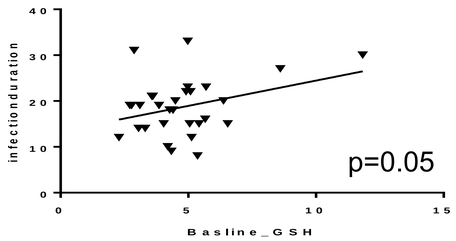
- Acutely HIV-infected participants enrolled in the SEARCH 010/RV254 study in Bangkok, Thailand were examined at baseline before combination antiretroviral therapy (cART), and at 6, 24, and 60 months after cART.
- HIV-uninfected healthy controls (HC) were recruited at the same site for comparison studies.
- Single voxel MRS was acquired on a 3T MR scanner, using short echo time (35ms) single voxel MRS.
- Two VOIs were acquired from the basal ganglia (BG) and the left frontal white matter (LFWM).
- LCModel was used to quantitate brain metabolites using GAMMA simulated reference basis sets.
- Neuropsychological tests including grooved Pegboard, Color Trails 1 and 2, Trailmaking A were performed at all visits. Z scores were averaged into an NPZ4-global score.
- Non-parametric statistical methods were used.

Participant Demographics

	HIV	HC
Sex (F/M)	1/52 at baseline 0/31 at 6 mo 0/18 at 24 mo 0/9 at 60 mo	7/8
Age (yrs)	24.9 (19-65)	31.6 (18-40)
Estimated duration of infection prior to cART, days	19 (8-50)	
CD4 count (cells/mm^2)	386 (137,1130)	
Log_{10} plasma HIV RNA, median (range)	6.1 (3.2,8.1)	

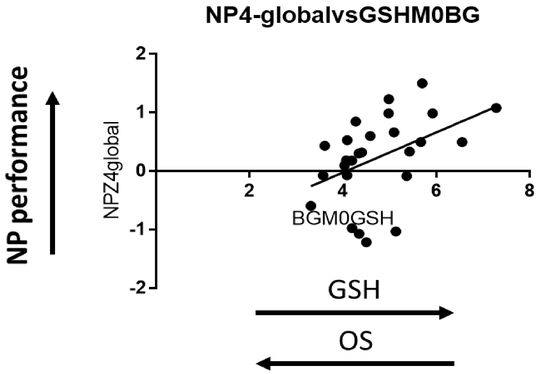
Results

1). Correlation of brain GSH in the basal ganglia with infection duration.



Results

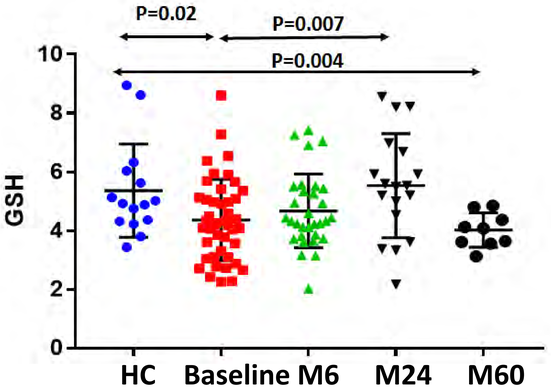
2). Baseline neuropsychological testing performance score (NPZ4-global) inversely correlated with oxidative stress in treatment naïve acute HIV infection.



Spearman correlation: r = 0.4728
95% confidence interval: 0.09267 to 0.7327
P (two-tailed) = 0.0147.

Results

3). Changes in GSH in the basal ganglia over four time points.



Brain GSH in acute HIV infection is significantly reduced compared to HC, P = 0.02 and elevated after 24 months of cART compared to baseline, P =0.007. After 60 months of cART, GSH is reduced compared to HC.

Conclusion

We demonstrated brain GSH can be measured using single voxel proton magnetic resonance spectroscopy approach. A reduction of cerebral GSH in naïve and treated HIV-infected participants supports the idea of glutathione metabolism dysfunction and persistent oxidative stress in HIV brain even after early ART. In our MRS scanning protocol, the two forms of glutathione, the reduced GSH and the oxidized glutathione (GSSG), exhibit very similar proton MRS spectra, therefore glutathione in this study represents total GSH levels. Further study is underway using the preferred J-editing method to better quantify GSH in human brain.

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