Plasma Heme Oxygenase-1 is Associated with Cognitive Decline in Children with HIV

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BACKGROUND

Heme oxygenase-1 (HO-1) is a detoxifying enzyme that has emerged as a critical effector for limiting cellular injury associated with oxidative stress and inflammation within the central nervous system (CNS) in several disease states, but has not previously been evaluated in children with HIV.

OBJECTIVES

- To determine whether plasma H0-1 levels differ between children with HIV and HIV-exposed uninfected controls.
- To determine if plasma HO-1 levels are elevated in subjects with cognitive decline.

METHODS

- Data and samples from two separate cohorts from IMPAACT 219C were evaluated.
- Subjects aged 6-16 with perinatal HIV (PHIV, 74 pre-cART and 75 post-cART) were first compared to age-matched HIV-exposed uninfected (HEU) controls (n=24).
- PHIV subjects with neurocognitive decline (drop in full scale IQ of 15 or more points) were compared to PHIV controls without decline (n=65 per group) .

RESULTS

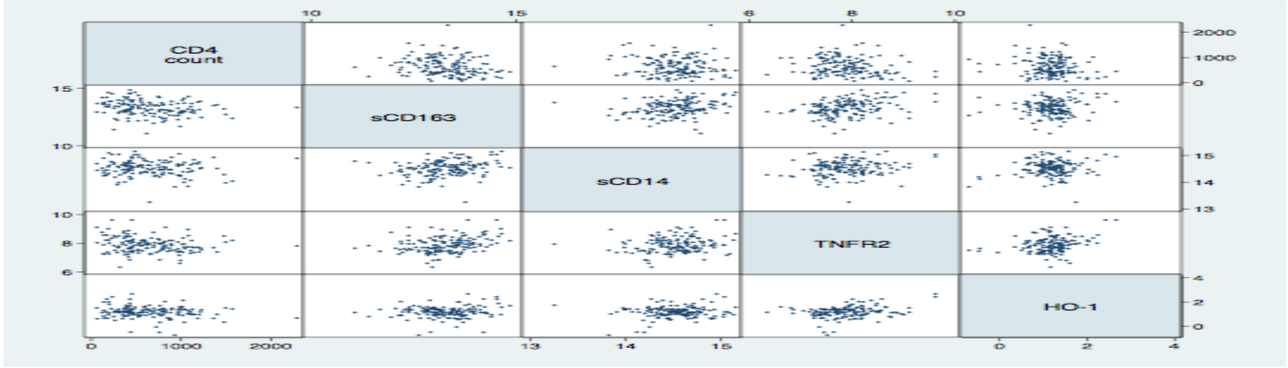
1. HO-1 levels are significantly elevated in PHIV compared to HEU subjects.
2. PHIV subjects in the highest quartile of HO-1 had increased risk of neurocognitive decline vs. those in the bottom three quartiles (OR 5.0, 95% CI 1.1-22.1, p=0.04).

CHARACTERISTICS of CASES and CONTROLS

Variable	Cases (n=75)	Controls (n=24)	P-value
Age at sample collection	10.8 (2.37)	9.2 (2.66)	**0.003***
Male sex	11 (46%)	27 (39%)	0.53
Black Race	42 (56%)	14 (58%)	0.66
Born in U.S.	66 (88%)	24 (100%)	0.08
Caregiver education<12 years	20 (32%)	10 (42%)	0.66

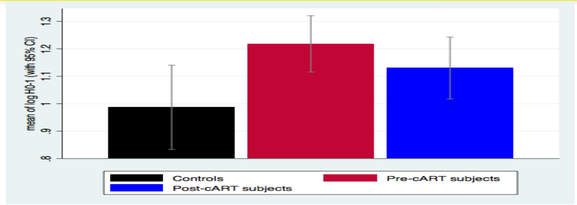
All variables are reported as mean (SD) or n (%). P-values <0.05 are in bold and marked with *.

CORRELATIONS WITH ADDITIONAL BIOMARKERS and CD4 COUNT

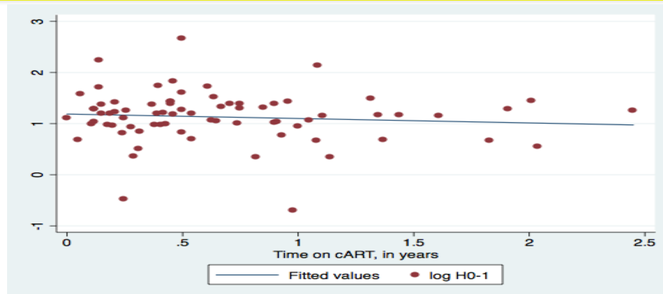


HO-1 levels correlated negatively with CD4 T-cell count (p = 0.04), and positively correlated with markers of macrophage activation, including sCD163 (p=0.001), sCD14 (p=0.04), and tumor necrosis factor receptor 1 and 2 (p<0.001).

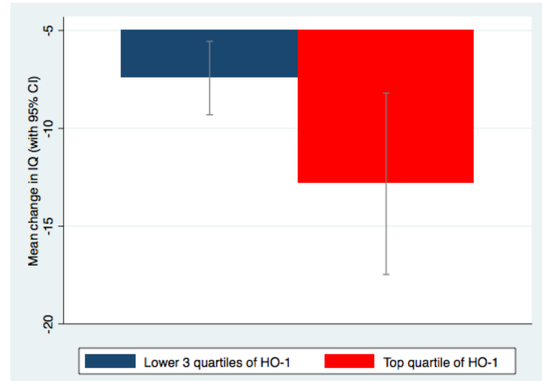
HO-1 LEVELS by CASE STATUS and TIME on cART



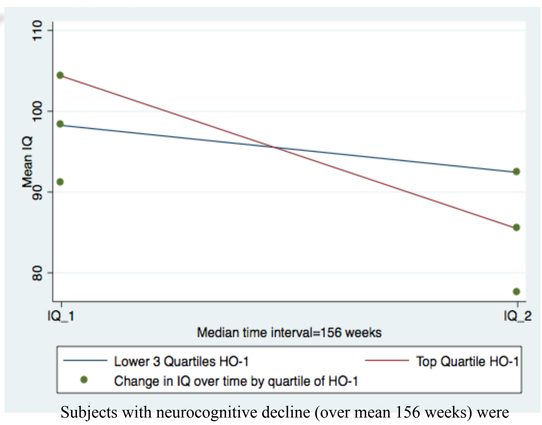
Pre-cART subjects had significantly higher HO-1 levels than HEU controls (3.71 vs. 2.88, p=0.01). Post-cART subjects had a slight decrease in HO-1 levels, but this decrease was not statistically significant, and there was no significant correlation between HO-1 levels and time on cART (p=0.4).



CHANGE in IQ, by HO-1 Quartile



Decrease in IQ was significantly greater for subjects in the highest quartile of H0-1 than those in the lower 3 quartiles (-12 vs. -7, p=0.02)



Subjects with neurocognitive decline (over mean 156 weeks) were significantly more likely to be in the highest quartile of H0-1.

CONCLUSIONS

- These results demonstrate a significant increase in HO-1 plasma levels in HIV infection and an association between HO-1 levels and cognitive decline.
- Plasma HO-1 may be a novel peripheral marker of HIV neuropathogenesis.

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