Abstract #1205

Plasma Soluble CD163 is Suppressed upon Early ART Initiation in Acute HIV Infection

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Background

Cognitive impairment (CI) persists in approximately 30-50% of chronically HIV-infected (CHI) individuals despite access to antiretroviral therapy (ART). Chronic inflammation, in part due to monocyte activation, correlates with poor cognitive performance, even in the case of viral suppression.

Plasma soluble (s)CD163, which is shed after monocyte/macrophage activation, is higher in cognitively impaired compared to unimpaired CHI adults on ART. Plasma sCD163 levels have also been shown to correlate with cerebrospinal fluid (CSF) neopterin, another biomarker of HIV-neuropathology and indicator of monocyte activation.

Whether early ART initiation in acute HIV-infection (AHI) impacts CD163 shedding is unknown.

Methods

Cohort Descriptions

High-risk participants were screened for AHI at The Thai Red Cross Anonymous Clinic. Participants were categorized into Fiebig I, Fiebig II, Fiebig III or Fiebig IV and immediately began ART. Controls included chronic HIV infected donors (CHI) (SEARCH 011, NCT00782808) and age-matched HIV-uninfected individuals (HIV- CO; SEARCH013) from Thailand.

Soluble monocyte biomarkers levels by ELISA

sCD163 and neopterin levels were measured by singleplex ELISA (Biorad and Genway, respectively) from plasma and CSF samples collected pre- and post-ART.

Immunophenotyping by flow cytometry

Cryopreserved peripheral blood mononuclear cells were stained with viability dye and antibodies against CD3, CD56, CD19, CD20 to exclude lymphocytes, natural killer and B cells, and HLA-DR, CD14 and CD16 to identify monocyte populations using flow cytometric analysis. The HLA-DR$^+$ cells were subset to delineate classical (CD14^{++}CD16$^-$), intermediate/inflammatory (CD14^{++}CD16$^+$) and non-classical/patrolling (CD14$^+$CD16$^+$) monocyte populations. Further staining allowed for the assessment of CD163. FlowJo software was used for cell gating.

Neuropsychological (NP) performance testing

NP tests included Trail Making A, Color Trails 1&2 and Grooved Pegboard to compute a summary NPZ-4. All raw scores were transformed to standard z-scores using Thai normative data.

Metabolite measurements by magnetic resonance spectroscopy (MRS)

Single-voxel proton MRS was used to measure brain metabolites (N-acetylaspartate (NAA), myoinositol (Ins), glycerophosphorylcholine (GPC), glutamate + glutamine (Glx) and creatine (Cr)) in 4 brain regions (basal ganglia (BG), frontal white matter (FWM), frontal grey matter (FGM) and posterior cingulate gyrus (PCG)).

Statistical analysis

Wilcoxon Rank Sum and Wilcoxon Signed Rank tests were used to compare within and between groups, respectively. Correlation analyses were assessed by Spearman correlations coefficients. Generalized Estimating Equation (GEE) model was used. Statistical analyses were performed using R v3.2.2.

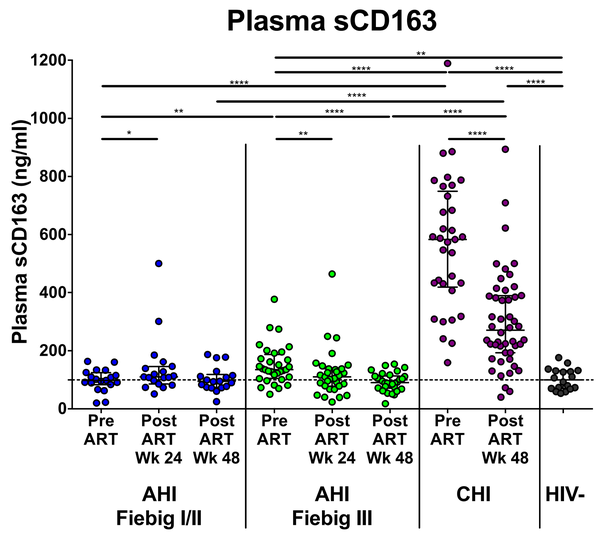
Results

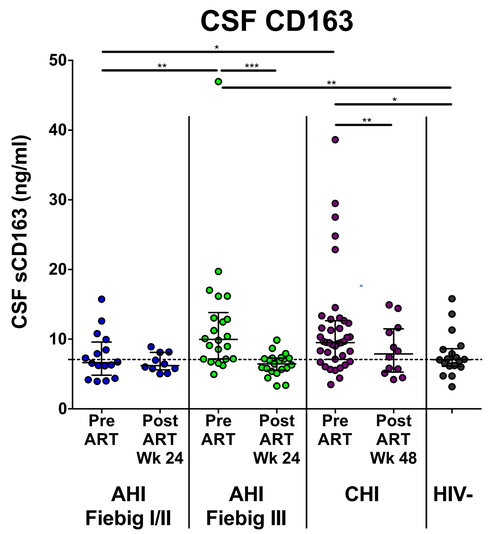
Median (IQR: 25, 75) except for gender	HIV-Uninfected n = 30	HIV-Infected Fiebig I/II (AHI) n =19	HIV-Infected Fiebig III (AHI) n =32	HIV-Infected CHI n = 53	P-value Comparing HIV+ groups
Gender (% male)	63.3%	94.7%	90.6%	45.3%	<0.0001
Age (years)	32.5 (26, 38)	31 (26, 39)	27.5 (23, 29)	34 (29, 37)	<0.0001
Education (years)	11 (8, 14)	18 (16, 20)	17 (14, 18)	11 (8, 14)	<0.0001
NPZ-4 score	0.23 (-0.13, 0.86)	-0.09 (-0.44, 0.17)	-0.22 (-0.49, 0.07)	-0.06 (-0.58, 0.31)	0.86
Log_{10} Viral Load (copies/ml)	-	5.08 (4.28, 5.54)	5.92 (5.52, 6.88)	4.85 (4.48, 5.50)	<0.0001
CD4 count (cells/μL)	-	447 (307, 567)	271 (228, 396)	228 (114, 353)	<0.0001

Demographic and clinical data

Results were analyzed using Chi-squared test for categorical and Kruskal-Wallis test for continuous variables.

1. sCD163 levels pre- and post- ART in Fiebig I/II AHI are comparable to levels observed in HIV-uninfected controls whereas in Fiebig III, a transient elevation in sCD163 is observed prior to normalization post ART. In CHI, sCD163 remain elevated despite ART.





2. Post-ART sCD163 levels in Fiebig I/II AHI did not associate with measures of CNS-related abnormalities.

Plasma sCD163

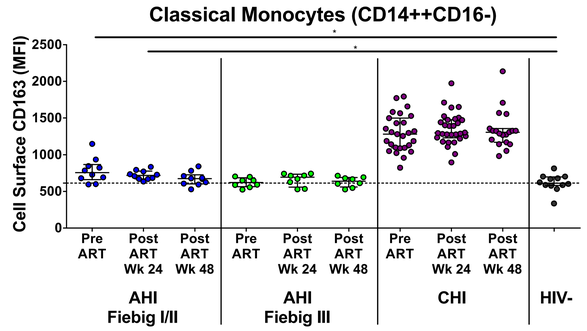
	AHI Stage	Plasma sCD163	Index of Brain Abnormality	Rho	P value
Pre-ART	Fiebig I/II	↑	↑ Grooved Pegboard Z Score Cognitive Performance	0.627	0.04
	Fiebig I/II	↑	↑ FWM Glx Neuronal cell function	0.709	0.003
	Fiebig III	↑	↓ PCG NAA Neuronal health	-0.468	0.02
Post-ART	Fiebig III	↑	↑ Neopterin Monocyte activation	0.399	0.03

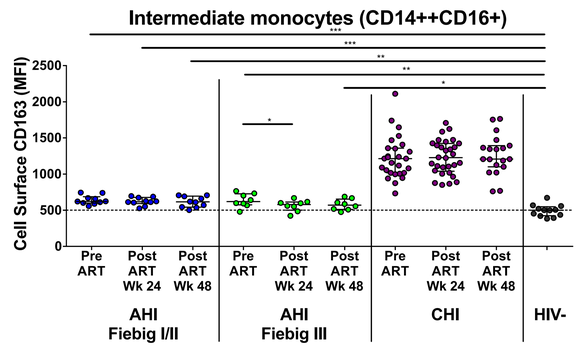
CSF sCD163

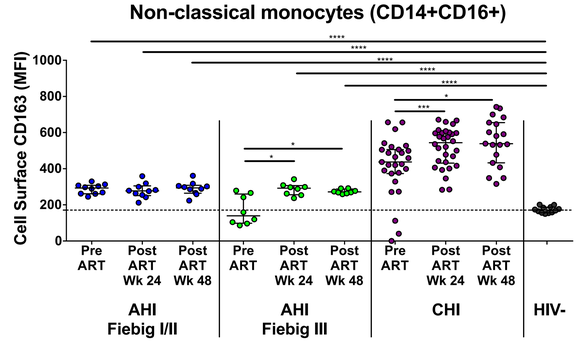
	AHI Stage	CSF sCD163	Index of Brain Abnormality	Rho	P value
Pre-ART	Fiebig I/II	↑	↓ BG Ins Astrocytosis and gliosis	-0.569	0.04
	Fiebig III	↑	↑ BG Cr Altered energy metabolism	0.518	0.02
	Fiebig III	↑	↑ BG GPC Cellular infiltration	0.472	0.04
	Fiebig III	↑	↑ Neopterin Monocyte activation	0.025	0.48
Post-ART	Fiebig III	↑	↓ NPZ-4 Score Cognitive Performance	-0.522	0.02
	Fiebig III	↑	↓ BG NAA Neuronal health	-0.500	0.03

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3. Surface CD163 levels on classical monocytes normalize after ART in AHI but remain elevated in CHI. Pre-ART, cell surface CD163 on CD16+ monocytes are dysregulated when compared to HIV-uninfected controls and persists despite ART.







Conclusion

- Early ART initiation led to normalization of both plasma and CSF sCD163 in AHI, irrespective of Fiebig stage, however sCD163 levels remained elevated in CHI when compared to HIV-uninfected controls.
- Post ART, in Fiebig III AHI, sCD163 levels correlated with several CNS-related abnormalities but not in Fiebig I/II.
- Pre-ART, dysregulated expression of CD163 on monocytes may reflect surface shedding presented as an elevation in plasma and CSF sCD163 during AHI and CHI compared to HIV- CO.
- **These data argue for the initiation of ART early in Fiebig I/II to limit CD163 shedding that appears related to neuro-inflammation and CNS related abnormalities.**