

# Astrocyte and microglial activation in acute and chronic HIV pre- and post-cART

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## Introduction

- HIV enters the central nervous system (CNS) during acute infection, initiating processes associated with HIV neuropathogenesis (1).

- YKL-40 (also termed chitinase-3-like protein 1 and human cartilage glycoprotein-39) is a systemic biomarker of inflammation & cancer.

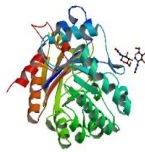


Figure 1. YKL-40 crystal structure.

- In the CNS, YKL-40 expression localizes to activated microglial cells and reactive astrocytes (2).

- CSF YKL-40 may predict development of Alzheimer's disease, multiple sclerosis, and SIV encephalitis (3-5).

- We sought to explore the impact of acute HIV infection and early versus later initiation of combination antiretroviral therapy (cART) on CSF YKL-40 levels and to correlate YKL-40 with markers of disease progression, neuroinflammation, and neuronal injury.

## Methods

**Study participants.** Thai individuals enrolled in Bangkok, Thailand in one of three groups:

- Acute HIV infection (AHI)
- Chronic HIV infection (CHI)
- HIV-uninfected controls (HIV-)

**Study design.** Participants underwent blood and CSF sampling, neuropsychological testing and magnetic resonance spectroscopy (MRS) imaging at enrollment (week 0/pre-ART) followed by immediate initiation of cART.

- Blood and CSF biomarkers, cerebral metabolites by MRS and neuropsychological performance were measured at:

- 0, 24, and 96 weeks in the AHI group
- 0 and 48 weeks in the CHI group
- 0 only in the HIV- group

- CSF YKL-40 was measured by ELISA (R & D Systems, Inc.) according to manufacturer's instructions.

**Analysis.** Cross-sectional analyses employed the Mann-Whitney U test and Spearman correlations; paired analyses were used to compare participants across time points.

## Results

	Acute HIV Infection (n=33)	Chronic HIV Infection (n=34)	HIV-Uninfected (n=18)	p-value (AHI vs CHI)
Age (years)	29 (24-37)	34 (29-36)	33 (27-39)	0.150
% Male	94	41	50	< 0.001
CD4 Count (cells/uL)	401 (318-568)	228 (146-342)	-	<0.001
Plasma HIV (log <sub>10</sub> copies/ml)	5.5 (4.9-6.3)	4.8 (4.4-5.3)	-	0.002
CSF HIV (log <sub>10</sub> copies/ml)	3.1 (1.7-4.3)	4.1 (3.7-4.8)	-	0.006
Estimated Duration Infection	18 (13-24) days	3.7 (0.9-6.4) years*	-	-
CSF WBC (cells/uL)	0 (0-3)	3 (2-9)	0 (0-0)	0.003
CSF Neopterin (nmol/L)	7.7 (4.7-13.5)	9.3 (7.0-13.0)	2.6 (1.9-2.9)	0.381
CSF Neurofilament (ng/L)	243 (204-333)	327 (251-568)	299 (210-337)	0.002
Typical cART Regimens	NNRTI-based cART +/- RAL/MVC	NNRTI-based cART	-	-

\* Duration of infection for chronic participants is time since diagnosis, and subject to recall bias.

Table 1. Comparison of baseline data at week 0 pre-cART visit for acute HIV, chronic HIV, and HIV-uninfected control participants.

### CSF YKL-40 Levels Pre-cART

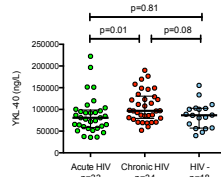


Figure 2. CSF YKL-40 at baseline, pre-ART in AHI participants (green circles), CHI participants (red circles) and HIV- uninfected controls (blue circles). Symbol convention is consistent in all figures

### CSF YKL-40 Levels Post- Suppressive cART

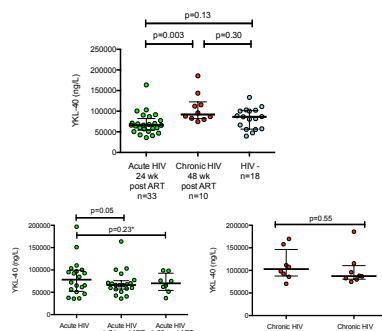


Figure 3 CSF YKL-40 across study groups after virologically-suppressive cART (top), and after cART in AHI (bottom left) and CHI (bottom right). Longitudinal analyses compare matched subjects.

### Baseline Pre-cART Correlations with CSF Biomarkers

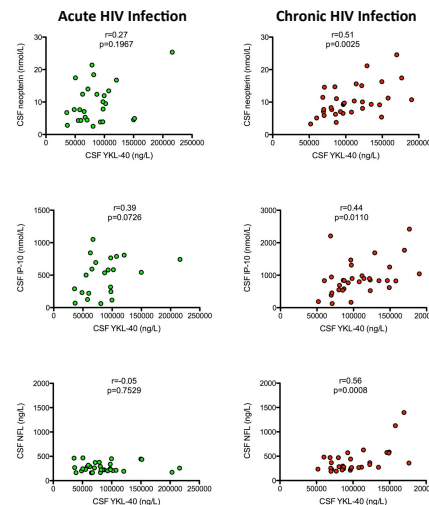


Figure 4. At baseline, CSF YKL-40 correlates with CSF IP-10 (lymphocyte chemokine) in AHI participants (green circles) and CSF neopterin (biomarker released by activated macrophages), CSF IP-10, and CSF neurofilament light chain (NFL, biomarker of axonal damage) in CHI participants (red circles), suggesting a relationship between neuroinflammation, astrocyte and microglial activation, and neuronal injury.

## Results (continued)

- No correlations were found between YKL-40 and markers of infection (CD4 T cell count, plasma HIV RNA, CSF HIV RNA) in either the acute or chronic HIV infection group at baseline or on-ART time points.

- No correlations between YKL-40 and neopterin, IP-10, and NFL were identified in the AHI group on-ART or in the CHI group on-ART, although the sample sizes were small (n=24 AHI at week 24; n=10 CHI at week 48).

- No correlations were identified with cerebral metabolites by MRS or neuropsychological performance in either the acute or chronic HIV infection group at either time point.

## Conclusions

- Pre-ART, elevations in CSF YKL-40 suggested that reactive astrocytes and microglial activation were present in chronic but not acute HIV infection.

- YKL-40 levels did not become elevated in AHI participants who immediately initiated cART.

- After suppressive cART, YKL-40 levels remained persistently elevated in CHI compared with AHI participants.

- YKL-40 correlated with neurofilament light chain in CHI, supporting a role for astrocyte and/or microglial activation leading to neuronal injury during CHI.

- Early cART initiation might reduce astrocyte and microglial activation and therefore might prevent or mitigate neuronal injury.

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