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

Michael Peluso[1], Victor Valcour[2], Jintanat Ananworanich[3], James Fletcher[4], Somporn Tipsuk[4], Bonnie Slike[3], Nittaya Phanuphak[4], Magnus Gisslén[5], Henrik Zetterberg[5], and Serena Spudich[6] on behalf of the SEARCH 010/RV254 Study Team

[1]Brigham and Women's Hospital, Boston, MA; [2]University of California-San Francisco, San Francisco, CA; [3]US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD; [4]SEARCH Thai Red Cross AIDS Research Center, Bangkok, Thailand; [5]University of Gothenburg, Gothenburg, Sweden; [6]Yale University, New Haven, CT

INHCC International NeuroHIV Cure Consortium

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.

• 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).

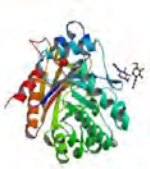

Figure 1. YKL-40 crystal structure.

• 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 enrolment (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 (log10 copies/ml)	5.5 (4.9-6.3)	4.8 (4.4-5.3)	-	0.002
CSF HIV (log10 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

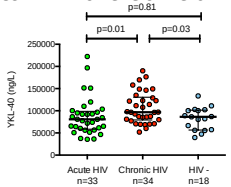

Figure 2. CSF YKL-40 at baseline, pre-ART in AHI participants (green circles), CHI participants (red circles) and HIV- uninfected controls (blue circles). Symbol convention is consistent in all figures

CSF YKL-40 Levels Post- Suppressive cART

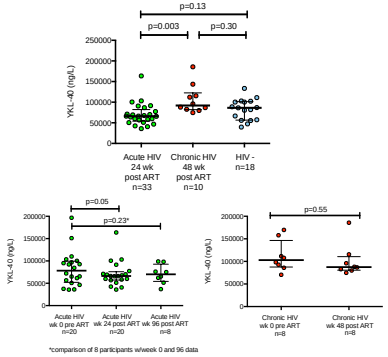

Figure 3 CSF YKL-40 across study groups after virologically-suppressive cART (top), and after cART in AHI (bottom left) and CHI (bottom right). Longitudinal analyses compare matched subjects.

Baseline Pre-cART Correlations with CSF Biomarkers

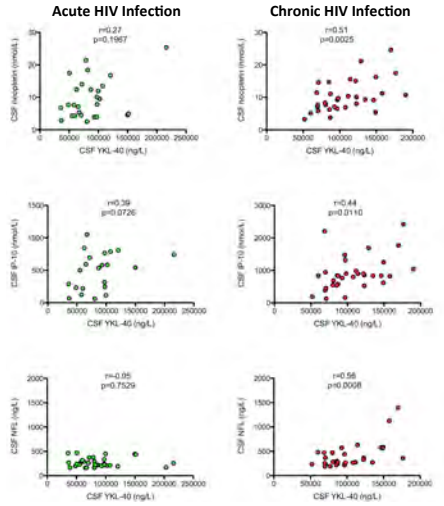

Figure 4. At baseline, CSF YKL-40 correlates with CSF IP-10 (lymphocyte chemokine) in AHI participants (green circles) and CSF neopterin (biomarker released by activated macrophages), CSF IP-10, and CSF neurofilament light chain (NFL, biomarker of axonal damage) in CHI participants (red circles), suggesting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

Acknowledgements

We gratefully thank the volunteers in SEARCH 010, 011 and 013; the staff at SEARCH Thailand and the Thai Red Cross AIDS Research Center; grants: W81XWH-11-2-0174, IAA between NIMH & NIAID AI502602; R01NS084911; R01MH095613; R21MH086341.

References

(1) Valcour et al. J Infect Dis 2012;206(2):275–82; (2) Bonneh-Barkay et al., *J Neuroinflammation* 2010; Jun 11;7:34; (3) Craig-Schapiro et al., *Biol Psychiatry.* 2010 Nov 15;68(10):903-12;(4) Bonneh-Barkay et al., *Am J Path* 2008 Jul;173(1):130-43; (5) Kolson. *Am J Path* 2008;173(1):25-29.

Disclaimer:

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.

MHRP US Military HIV Research Program

SEARCH

UCSF

Yale University School of Medicine