CROI 2020
March 8-11
Boston, MA

Evolution of Immune Activation Biomarkers in CSF in Fiebig I-V Acute HIV Infection and HIV-Negative Controls

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Julian J Weiss[1], Phillip Chan[2], Carlo Sacdalan[2], Eugene Kroon[2], Siriwat Akapirat[3], Jennifer Chiarella[1], Victor Valcour[4], Nittaya Phanuphak[2], Ningbo Jian[5,6], Sandhya Vasan[5,6], Jintanat Ananworanich[2,5,6], Bonnie Slike[5,6], Shelly Krebs[5,6], Serena Spudich[1] on behalf of the RV254/SEARCH 010 study.

[1]Yale School of Medicine, New Haven, CT, USA. [2]SEARCH, Thai Red Cross AIDS Research Centre, Bangkok, Thailand. [3]Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand. [4]Memory and Aging Center, Department of Neurology, University of California San Francisco, CA, USA. [5]U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA. [6]Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. Bethesda, MD, USA.

INHCC International NeuroHIV Cure Consortium

Background

- There is a rapid, broad induction of numerous antiviral and proinflammatory biomarkers in acute HIV infection (AHI)
- Studies suggest that plasma biomarker expression in AHI occurs in ordered patterns and waves
- Initial CNS immune response may set the trajectory for disorders relating to HIV-associated neurocognition
- Early neuroinvasion and immune responses in AHI may be important in setting the trajectory for neuronal injury and cognitive impairment in HIV-associated neurocognitive disorder (HAND)

Objectives

1. To investigate profiles of immune activation and inflammatory markers in the CSF (cerebrospinal fluid) within SEARCH 010/RV254 AHI (Fiebig I-V) participants and compared to HIV-negative controls
2. To use these profiles to better understand the dynamics of immune activation pathways in the CNS during AHI

Methods

Study Participants

- Individuals with AHI (Fiebig I-V) were enrolled in a longitudinal observational study (RV254/SEARCH 010) with baseline blood sampling and clinical characterization in Bangkok, Thailand
- Individuals without HIV were enrolled in a separate but similar protocol for controls

Data Collected

- Sex, age, and duration of HIV infection were obtained at baseline using standardized study questionnaires
- Laboratory evaluations were completed at baseline and included CD4 count, plasma viral load, and CSF viral load
- Laboratory evaluations, including P24 antigen and HIV-1-specific antibody, were used to assess Fiebig stage
- 41 CSF biomarkers of immune activation were analyzed using Luminex or ELISA

Statistical Analyses

- Temporal expression patterns visualized by heatmap analysis
- Pathway kinetics identified through hierarchical clustering using non-parametric correlation of biomarkers differentially expressed between Fiebig stages (Spearman's correlations)
- Post-hoc Dunn's test performed as a confirmatory test to quantify the heatmap data and adjust for multiple comparisons

Disclaimers

The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above, the U.S. Department of the Army or the U.S. Department of Defense, the Henry M. Jackson Foundation for the Advancement of Military Medicine, the National Institutes of Health, the Department of Health and Human Services, or the United States government, nor does mention of trade names, commercial products, or organizations imply endorsement by the Thai Red Cross AIDS Research Centre. The investigators have adhered to the policies for protection of human participants as prescribed in AR-70-25.

Acknowledgements

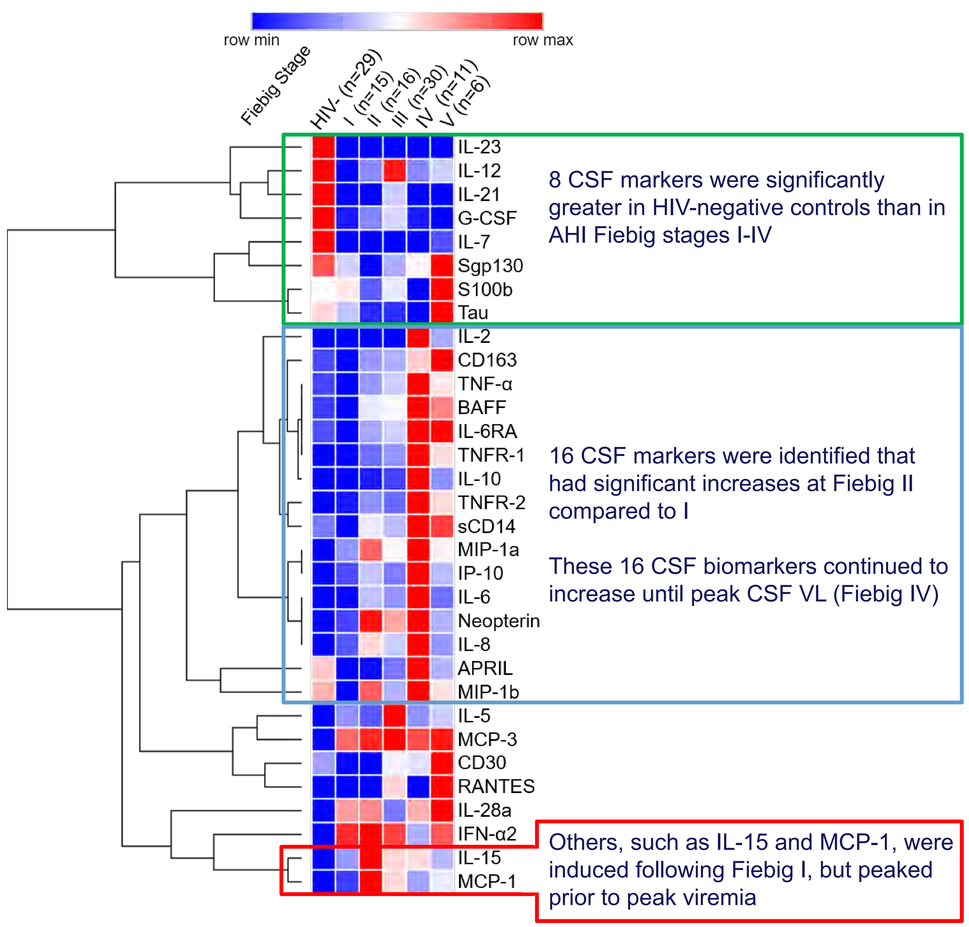
We would like to thank the study participants from the RV254/SEARCH 010 study, which is supported by cooperative agreements (WW81XWH-18-2-0040) between the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and the U.S. Department of Defense (DOD) and by an intramural grant from the Thai Red Cross AIDS Research Centre. This research was funded, in part, by the U.S. National Institute of Allergy and Infectious Diseases and by the National Institute of Mental Health (through R01MH095613 and R01MH106466, and support for the International NeuroHIV Cure Consortium), with added support from the G. D. Hsiung, PhD Student Research Fellowship and the IDSA/HIVMA GERM Medical Student award.

Results

TABLE 1. Demographics and Clinical Characteristics

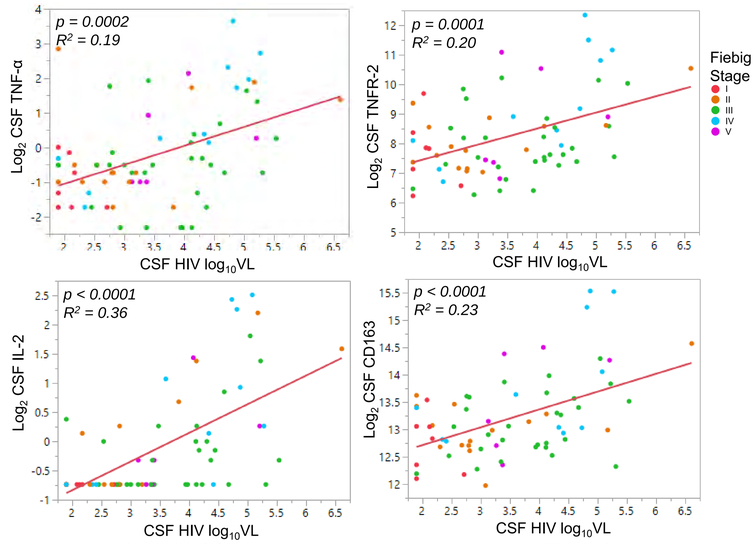
	AHI (n = 78)	HIV-negative (n = 29)	p-value
Age, years	28 (23-33)	31 (26-39)	0.01
Male sex, n (%)	77 (99)	18 (62)	<0.0001
Blood CD4+ T-lymphocytes, cells/ µL	400 (280-543)	933 (764-1173)	<0.0001
Plasma HIV RNA, log_{10} copies/mL	5.69 (5.01-6.51)		
CSF HIV RNA, log_{10} copies/mL	3.37 (2.58-5.18)		
CSF HIV RNA < 80 copies/mL, n (%)	10 (13)		
Estimated days of infection, days	18 (15-23)		
Fiebig stage, n (%)			
I	15 (19)		
II	16 (21)		
III	30 (38)		
IV	11 (14)		
V	6 (8)		

FIGURE 1. Hierarchical clustering of CSF biomarker levels by HIV status and Fiebig stage



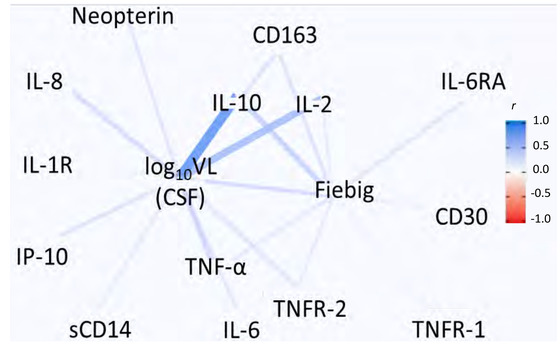
Results

FIGURE 2. Correlation of CSF biomarkers and CSF HIV RNA



- Most of the 16 CSF biomarkers that were greatest at Fiebig IV had positive correlations with CSF HIV viral load
- Above are four representative biomarkers that illustrate this correlation with viral load

FIGURE 3. Network analysis of correlation between Fiebig stage and CSF viral load, and each CSF marker (FDR-adjusted)



p < 0.05, adjusted for false discovery rate

- non-significant correlations are dropped from plot

Conclusions

- There are **temporal pathways** of multiple CSF biomarkers with *differential dynamics of immune activation* during AHI
- Predominant pattern: Fiebig II > Fiebig I, with peak biomarker concentration occurring at peak CSF HIV RNA level (Fiebig IV)
  - These biomarkers are largely **proinflammatory cytokines**, and levels correlate with CSF HIV RNA
- Further studies are needed to explore whether these early immunological mechanisms contribute to HAND