Peripheral Immune Activation Modulates HIV RNA Entry to CSF in Early Acute Infection

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ABSTRACT

The mechanisms determining the magnitude of initial HIV entry into the nervous system during acute HIV infection (AHI) are largely unknown. We examined whether peripheral blood and mucosal cellular immune activation were independently associated with the level of HIV RNA detected in cerebrospinal fluid (CSF) during the earliest stages of HIV infection (Fiebig I to III).

Concurrentblood, CSF and sigmoid biopsy samples wereobtained at thetime of AHI diagnosis (8 Fiebig I, 11 Fiebig II and 19 Fiebig III) in the context of an observational study of AHI in Bangkok, Thailand (RV254/SEARCH 010). CSF and plasma HIV RNA levels were measured by Roche Amplicor HIV-1 Monitor and Roche COBAS TaqMan HIV-1 tests. Multiparameter flow cytometry was performed using frozen and fresh samples to determine systemic and mucosal immune activation ($Ki67^+$ and $CD38^+$/$HLA\text{-}DR^+$), respectively. CSF chemokine levels (IP-10 and neopterin) were quantified by ELISA. Mann Whitney U test was used for comparisons and linear regression and Pearson's Correlation to evaluate associations.

Among 38 early AHI subjects, 90% were MSM, the median age was 29 years, mean CD4 count was 438 cells/mm^3, and estimated duration since exposure was 15 days. During early AHI, plasma ($p<0.001$) and CSF HIV RNA ($p<0.001$), CSF neopterin levels ($p=0.003$) and the frequency of activated $CD8^+$ T cell in blood ($p=0.002$) and sigmoid mucosa ($p<0.001$) increased with progression from Fiebig I to Fiebig III. In univariate analyses of the overall group, CSF HIV RNA was associated with CSF IP-10 levels ($r=0.37$, $p=0.04$), CSF neopterin levels ($r=0.61$, $p<0.001$), the frequency of $CD8^+Ki67^+$ T cells in the blood ($r=0.56$, $p=0.001$) and the frequency of $CD8^+Ki67^+$ ($r=0.48$, $p=0.008$) and $CD8^+CD38^+HLA\text{-}DR^+$ ($r=0.46$, $p=0.01$) T cells in the mucosa. Moreover, when adjusting for levels of plasma HIV RNA, the frequency of peripheral $CD8^+Ki67^+$ T cells remained a significant predictor of CSF HIV RNA (adjusted $r=0.78$, $p<0.001$).

During early AHI, CSF inflammation and peripheral and mucosal immune activation are present and increase with progression of Fiebig stage from I to III. The correlation between CSF HIV RNA and frequency of activated $CD8^+$ T cells in the blood independent from plasma HIV RNA supports the hypothesis that peripheral immune activation modulates the amount of HIV entering the CNS during this earliest stage of infection.

BACKGROUND

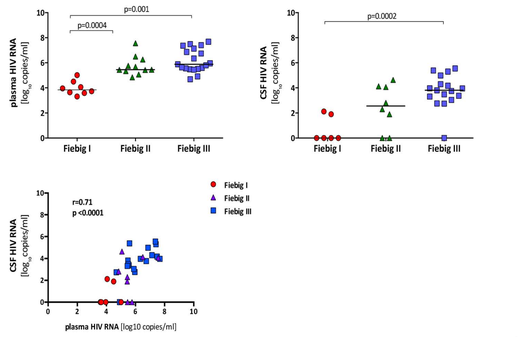
- $CD8^+$, and to a lesser extent $CD4^+$, T cell activation is a strong predictor of CD4 T cells loss and overall prognosis of HIV-1 infection
- Attenuation of immune activation may be an important contributor to treatment responses *(Deeks, Blood, 2008)*
- Peripheral, mucosal and CNS inflammation occurs early during acute HIV-1 infection, with CSF HIV RNA detectable as early as 8 days after exposure *(Valcour, JID, 2012; Schuetz, PLoS Pathogens, 2014)*
- NHP studies have shown that events early during infection negatively impact long-term cognition *(Fuller et al., 2004, BMC Neurosci)*
- In chronic HIV infection the level of systemic immune activation can modulate CSF HIV-1 replication, due to the trafficking of infected cells in the CNS compartment *(Sinclair, J AIDS, 2008)*

COHORT CHARACTERISTICS

Baseline Characteristics	Fiebig I (n=8)	Fiebig II (n=11)	Fiebig III (n=19)
Age [years]	35 (29 - 42)	25 (23 - 30)	29 (24 - 32)
Male:Female	7:1	11:0	17:2
MSM, n (%)	7 (88)	11 (100)	16 (84)
Days since HIV infection	14 (10.5 - 16)	14 (8 - 18)	16 (13 - 21)
HIV subtype			
CRF01_AE	8 (100)	9 (82)	15 (79)
B	-	1 (9)	1 (5)
CRF01_AE/B Recombinant	-	1 (9)	3 (16)
CD4 count [cells/mm^3]	603 (541 - 810)	339 (269 - 555)	389 (341 - 532)

RESULTS

Plasma and CSF HIV RNA Increase with Progression of Fiebig Stage and are Strongly Correlate



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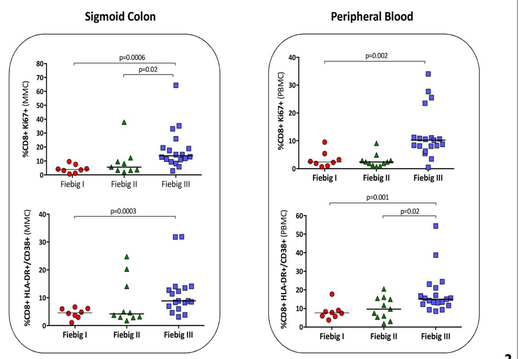
Systemic and Mucosal Immune Activation Increase with Progression of Fiebig Stage



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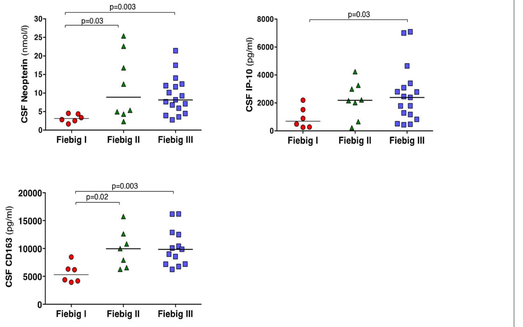
CNS Inflammation Increases with Progression of Fiebig Stage



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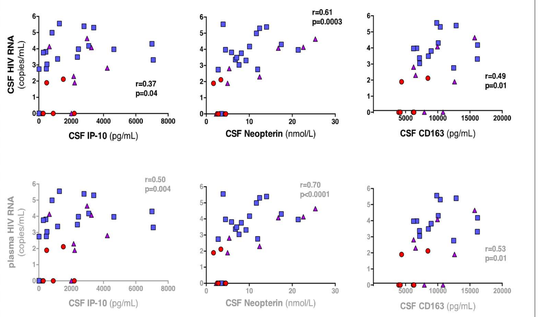
Immune Activation in the CSF Correlated with HIV RNA in the CSF and the Plasma



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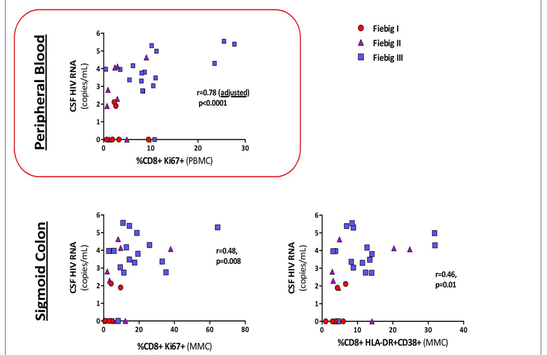
Systemic Immune Activation Levels, Adjusted for Plasma HIV RNA, were Highly Predictive for CSF HIV RNA



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QUESTION

Does peripheral and/or mucosal immune activation of $CD8^+$ T cells during early acute HIV-1 infection influence HIV RNA entry into CSF?

CONCLUSION

- CNS inflammation and peripheral and mucosal immune activation are present in early acute HIV infection and increase with progression of Fiebig Stage
- Univariate analysis showed that markers of CNS inflammation as well as peripheral and mucosal immune activation correlate with CSF HIV RNA
- Moreover, activated $CD8^+$ T cells in the blood correlated with CSF RNA independent from plasma HIV RNA, supporting the hypothesis that peripheral immune activation modulates the amount of HIV entering the CNS during earliest stages of HIV infection

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.