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INTRODUCTION

Host immune activation is a critical factor in systemic disease progression in HIV/AIDS. Cerebrospinal fluid (CSF) neopterin, derived from activated macrophages and microglia, reflects intrathecal immunoreactivation. Elevated CSF neopterin levels are associated with progression of CNS injury in HIV-infected individuals.

Antiretroviral therapy (ART) which fails to completely suppress plasma viremia may have benefit in relation to the progression of systemic HIV, but the effects of failed therapy in the CNS compartment are unknown.

We undertook a study to measure the CSF and blood neopterin levels in defined groups of subjects to test the hypothesis that CNS immunoreactivation is reduced in treated subjects with virological failure as compared to subjects off of therapy.

STUDY DESIGN AND METHODS

Cross-sectional study comparing laboratory and clinical data from four groups of participants categorized by HIV infection status, antiretroviral treatment status, and plasma HIV RNA viral load (VL):

HIV infected subjects -

- **Offs** not taking ART for ≥ 4 months
 - **Failures** on ART with plasma VL ≥ 500 copies/mL
 - **Successes** on ART with plasma VL < 500 copies/mL
- HIV negative subjects for background laboratory values

CSF was obtained via lumbar puncture for study purposes rather than for clinical diagnosis; paired plasma samples were obtained at concurrent study visits. Informed consent was obtained from all subjects.

Neopterin was measured by the ELitest Neopterin EIA (BRAHMS, Berlin, Germany). In samples with HIV RNA levels < 50 copies/mL, HIV VL was measured by an UltraUltrasensitive modification of the Roche Amplicor HIV 1 Monitor assay with a quantitation limit of 2.5 copies/mL.

Results were analyzed with the one-way ANOVA, followed by the Tukey post-hoc test for individual group comparisons.

RESULTS

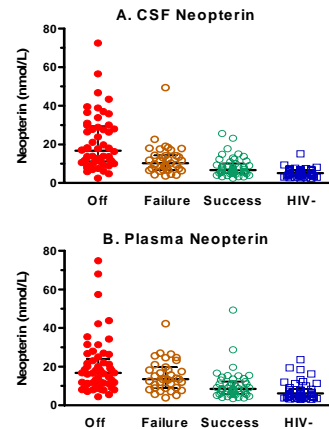
Table 1. Demographic and Treatment Characteristics of Subjects

	Subject Group			
	Offs n=57	Failures n=35	Successes n=47	HIV Negatives n=48
Sex (M:F)	49:8	31:4	43:4	40:8
Age in Years	41.5 (+/- 5.9)	42.5 (+/- 5.6)	43.1 (+/- 6.8)	44.2 (+/- 8.8)
Years Since Diagnosis	9.9 (+/- 6.1)	13.0 (+/- 4.1)	11.7 (+/- 5.5)	NA
Total Number ART Medications	0.0	3.4 (+/- 1.0)	3.4 (+/- 0.8)	NA
Treatment Duration (months)	NA	26.8 (+/- 24.8)	30.8 (+/- 30.2)	

ART, antiretroviral therapy. Values shown are means (+/- SD) except where noted.

Demographics and treatment history did not differ significantly between the HIV-infected groups, except for years since diagnosis in the Offs versus Failures groups ($p = 0.029$, Tukey). Of the Offs group, 35% (20/57) were naive to ART; those previously treated had been off for an average of 29.9 months (SD 33.5).

Figure 1. CSF and Plasma Neopterin Concentrations for Subjects in Each Group



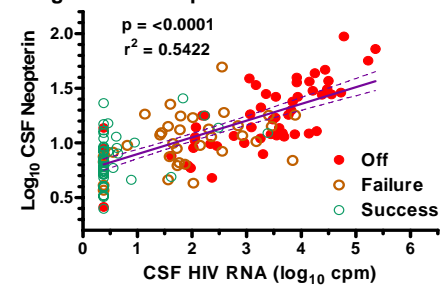
A. See Table 2 for group comparisons. CSF neopterin concentrations were lower in the Failures group as compared with the Offs group, despite similar CD4 counts and plasma HIV VLs in the two groups. The median value of CSF neopterin in the Failures group was similar to that in the Successes group, though not reduced to the level of the HIV negatives group. There was no difference between CSF neopterin levels in the HIV negatives group and the Successes group. **B.** Results for plasma neopterin were similar except that concentrations measured in the Failures group were higher than those in the Successes.

Table 2. Laboratory Results

	Subject Group				Significant Differences
	1. Offs	2. Failures	3. Successes	4. HIV Negatives	
CD4 (cells/mL)	343.0 (215.0 - 500.0)	247.0 (129.0 - 350.0)	321.0 (232.0 - 581.0)	839.0 (661.0 - 1064.0)	(4: 1, 2, 3)
VL Plasma (log)	4.42 (3.61-4.96)	3.92 (3.24 - 4.92)	0.86 (0.38 - 1.94)	NA	(3:1, 2)
VL CSF (log)	3.48 (2.35 - 4.14)	1.78 (1.44 - 2.55)	0.38 (0.38 - 0.49)	NA	(1:2,3)
CSF Neopterin (nmol/L)	16.8 (11.1 - 29.7)	10.3 (6.9 - 14.4)	6.7 (5.2 - 10.1)	5.2 (3.7 - 6.7)	(1: 2, 3, 4; 2: 4)
Plasma Neopterin (nmol/L)	16.8 (11.3 - 24.5)	13.5 (8.9 - 14.4)	8.5 (5.9 - 12.3)	6.1 (4.3 - 8.3)	(1: 2, 3, 4; 2: 3, 4)

Data are reported as median and intraquartile range. Analysis was performed by ANOVA followed by Tukey. Significant differences ($p < 0.05$) between groups are denoted by group numbers separated by colons versus commas.

Fig 2. CSF Neopterin in Relation to CSF VL



CSF neopterin concentration correlated with CSF HIV VL in the three HIV-infected groups. CSF neopterin and HIV VL were log transformed for analysis. The reduction of CSF neopterin in Failures compared to Offs was present across the range of plasma HIV VL (data not shown).

CONCLUSIONS

• Antiretroviral therapy that fails to completely suppress systemic HIV successfully down-regulates local macrophage activation in the CNS seen in HIV-infected patients off of therapy.

• CSF neopterin levels correlate with CSF HIV viral load in subjects on and off of therapy, supporting an association between CSF HIV RNA concentration and neuropathogenesis in the CNS.

• Inhibition of intrathecal immune activation by ART, even in the absence of complete plasma HIV suppression, may prevent or ameliorate the neuropathogenesis of HIV.

ACKNOWLEDGEMENTS: This work was supported by: NIH R01 NS37660, R01 MH62701, MO1-RR-00083.

