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ANTIRETROVIRAL TREATMENT INITIATED AT HIGH CD4 CELL COUNTS DOES NOT NORMALIZE CEREBROSPINAL FLUID MARKERS OF IMMUNE ACTIVATION

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Background

HIV infects cells in the central nervous system (CNS), mainly microglia and perivascular macrophages, and induces a chronic intrathecal immune activation. Similar to its effect outside the CNS, antiretroviral treatment (ART) substantially decreases CNS inflammation and CD4+ T-cell trafficking through the cerebrospinal fluid (CSF) is often reduced to near normal levels. However, CSF levels of neopterin, a pteridine marker of primarily macrophage/microglia activation, have been found to be slight increased in the majority of persons living with HIV (PLWH) who begin treatment during the chronic phase of HIV infection when the immune function is impaired *(Ulfhammer et al AIDS 2018, 32:2171)*. By contrast, CSF neopterin is essentially normalized when ART is initiated early, during acute HIV infection (AHI)*(Hellmuth et al J Infect Dis, 220, 12: 1885)*. The aim of this study was to evaluate if CSF immune activation biomarkers normalize to a larger extent in PLHIV with chronic HIV who start ART at high, as compared to starting treatment at low CD4-cell counts.

Methods

176 neuro-asymptomatic patients who started ART during chronic HIV were retrospectively included from the longitudinal prospective Gothenburg CSF cohort study and followed for in median 5.0 (mean 6.1) years. Lumbar punctures were performed at baseline before ART, after 1, and >3 years on suppressive treatment. Twenty-two participants had a CD4 cell nadir <50; 31 between 50 and 199; 32 between 200 and 349; 13 between 350 and 499; and 13 ≥500 cells/μL. Neopterin concentrations were measured using a commercially available immunoassay (NEOPT-SCR.EIA 384 Det., Thermo Fisher Scientific – BRAHMS GmbH, Henningsdorf, Germany) with an upper normal reference value of 5.8 nmol/L in CSF *(Hagberg et al AIDS Research and Therapy 2010, 7:15)*. Patient baseline characteristics are presented in **Table 1**.

Results

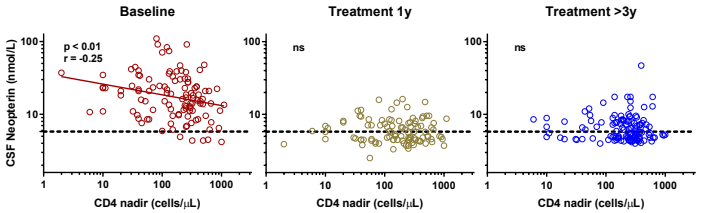


Figure 1. A significant inverse correlation between CD4 cell count and CSF neopterin was found at baseline (r = -0.25, p < 0.01) while no correlations between CD4 nadir and CSF neopterin were found after 1, or >3 years ART.
The persons with high CD4 nadir did not normalize their CSF Neopterin despite having lower neopterin levels from start.

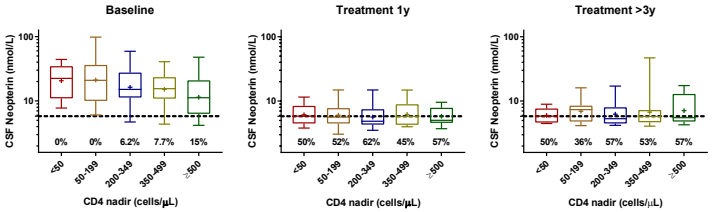


Figure 2. 15% of participants with the highest CD4 nadir (>500) had normal CSF neopterin (<5.8 nmol/L) compared to 0% of those with the lowest CD4 nadir (<50). After 1 and respectively >3 years of ART, no difference was seen between the groups.
Even the groups with higher CD4 cell nadir did not normalize CSF neopterin levels.

Discussion

In contrast to ART initiation during acute HIV-infection, chronically HIV-infected patients starting ART at high CD4 cell counts do not normalize the macrophage/microglial activation marker CSF neopterin to any greater extent than if treatment is started later with low CD4 cell counts. This may reflect the inability of ART to affect the CNS reservoir that has been established already before the early phases of the chronic infection.

CD4 nadir cell count, 10^6 cells/L (mean)	n (176)	Age y(range)	P-HIV- RNA log10 Median copies/mL	CSF HIV-RNA log10 Median copies/mL	CSF Neopterin Log10 Median nmol/L
>=500 (677)	16	45 (25-55)	4.5 (2.7-6.1)	3.7 (1.0-5.4)	1.1(0.6-1.7)
350-499 (419)	22	44 (18-69)	4.5 (3.6-5.6)	3.6 (2.5-5.4)	1.9(0.6-1.7)
200-349 (267)	61	38 (19-64)	4.5 (2.5-6.3)	4.1 (1.0-5.5)	1.1(0.6-2.0)
50-199 (120)	52	41 (18-68)	5.1 (4.0-6.1)	4.2 (1.0-5.4)	1.3(0.8-2.0)
<50 (27)	25	43 (27-70)	5.4 (4.1-6.0)	2.9 (1.0-4.8)	1.4(0.9-1.6)

Table 1: Characteristics of participants.

-CSF NEOPTERIN DOES NOT NORMALIZE IN MANY PATIENTS INITIATING ART DURING CHRONIC HIV

-THIS ALSO APPLIES TO WHEN ART IS INITIATED AT HIGH CD4 CELL COUNTS

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