O3. Mild neurocognitive impairment is associated with CNS immunoactivation and neuronal injury in HIV-infected patients on effective antiviral therapy

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Background
Even in patients responding well to current antiretroviral therapy (ART), HIV-associated neurocognitive disorders (HAND) remain prevalent. However, it is unclear if neuronal damage continues despite effective suppression of HIV-1. The light subunit of the neurofilament protein (NFL) is a component of myelinated axons, and elevated concentrations in cerebrospinal fluid (CSF) are a sensitive marker of ongoing axonal injury in HIV-associated dementia (HAD). To investigate if milder forms of neurocognitive impairment – asymptomatic neurocognitive impairment (ANI) and minor neurocognitive disorder (MND) – are associated with ongoing neuronal damage, we analyzed CSF NFL in a well characterized cohort of virally suppressed subjects on ART with or without ANI/MND.

Methodology
In a cross-sectional analysis, subjects on ART with plasma HIV-1 RNA <50 c/ml without significant confounding conditions (e.g., current substance dependence) were identified from longitudinal studies (CHARTER and HNRC). Standardized neurocognitive performance (NP) testing was performed. Subjects were classified as NP-normal (NPN) or neurocognitively impaired (NCI) based upon demographically-adjusted norms. The NCI group included subjects with asymptomatic neurocognitive impairment (ANI) or mild neurocognitive disorder (MND). Subjects were selected to yield approximately equal samples of NPN, ANI, and MND, and were evaluated on two separate occasions. Subjects were also categorized according to the stability of their NP test performance. CSF concentrations of NFL were measured by an enzymatic 2-site quantitative immunoassay (UmanDiagnostics, Umea, Sweden). CSF neopterin was measured by ELISA. Continuous variables were log10 transformed where appropriate. For two group comparisons, Mann- Whitney-U-test was used. Correlations were calculated using Pearson correlation coefficients test.

Results
100 (91% male) subjects were included in the analysis, 29 NPN and 71 with NCI (ANI=38; MND=33). Median (IQR) age at inclusion was 47 (41-54) years, with current CD4+ 524 (359-771) and nadir 72 (10-224) x106 cells/l. Subjects with NCI had higher CSF NFL than the NPN group at inclusion (NCI median 592, IQR 372-770; NPN median 462, IQR 364-553; p=0.06) and follow up (NCI median 562, IQR 388-774; NPN median 435, IQR 375-535; p=0.02). We found no correlation between CD4 cell count or CD4 nadir and NFL, however CSF neopterin was significantly correlated to NFL in the whole study population (r=0.21; p=0.035) and CSF neopterin was higher in the NCI group than in the NPN group at inclusion (NCI median 7.3, IQR 4.9-12; NPN median 4.8, IQR 4.7-7.4 nmol/l; p<0.01) as well as at follow up (NCI median 6.3, IQR 4.8-10.6; NPN median 4.9, IQR 4.6-7.2; p<0.05). We found no difference in CSF biomarkers between subjects with stable or declining NP test results.

Conclusions
In this analysis, we found signs of increased CSF NFL as well as CSF neopterin in subjects with mild compared to subjects without neurocognitive impairment, indicating an association between increased intrathecal immune activation, neuronal damage and neurocognitive impairment in patients on ART.