Background: HIV central nervous system (CNS) infection is associated with local inflammation that evolves over the course of systemic disease and impacts neurological function. To compare CNS and systemic inflammation, we assessed 10 inflammatory biomarkers in cerebrospinal fluid (CSF) and blood across a spectrum of subject groups.

Methodology: This exploratory cross-sectional study measured 10 inflammatory biomarkers (TNF-α, MMP-9, CXCL10, sCD14, sCD163, sVCAM, CCL2, IL-6, TIMP-1 and neopterin) by EIA in 9 subject groups: HIV uninfected controls (HIV-, N=20); primary HIV infection (PHI, 24); untreated neuroasymptomatic subjects in 4 blood CD4+ cell strata, >350, 200-349, 50-199 and <50 cells/μL (NA, 20 each); untreated HIV-associated dementia (HAD, 12); treated, virally-suppressed (Rx, 19) and elite controllers (EC, 8). Exploratory analysis applied nonparametric methods to a priori group comparisons: PHI to HIV-; across the 4 NA groups; HAD to combined subject groups with <200 CD4 cells/μL; and Rx and EC to HIV (significance set at P<0.05). Relationships among CSF and blood biomarkers along with background variables including CSF neurofilament light chain protein (NFL) across the entire sample set were explored by Spearman correlation.

Results: CSF and blood showed a broad increase in inflammatory biomarker concentrations in PHI with increases in TNFα, CXCL10, sCD14 and neopterin in both compartments, sVCAM in CSF, and sCD163 in blood. With progression of systemic disease, patterns of biomarker changes in the four NA groups diverged between CSF and blood. Whereas CSF concentrations of TNFα, MMP-9, CXCL10 decreased in the CD4 <50 group compared to one or more groups with higher CD4 counts, blood inflammatory biomarkers either increased with falling CD4 or remained relatively stable across the four groups, with the exception of MMP-9 concentrations which progressively decreased. CSF concentrations of all the inflammatory biomarkers except MMP-9 were higher in the HAD than the combined <200 CD4 groups. By contrast, blood concentrations did not differ between these two groups. CSF blood markers remained above HIV- levels in the Rx and EC groups including: CSF TNFα, CXCL10, sCD14, sCD163 and sVCAM in Rx and all of these except sVCAM in EC; blood sCD14, CCL2 and neopterin in Rx; and blood CXCL10, sCD163 and TIMP-1 in EC. CSF NFL showed highest correlations with CSF sCD14, sCD163, sVCAM, CCL2 and blood sCD14 and neopterin (all R>0.5).

Conclusions: Early parallel increases in CSF and blood inflammatory biomarkers diverge with evolving infection and HAD onset, and support the importance of macrophages in neural injury. Persistent CSF and blood inflammation despite viral suppression suggest incomplete - or a required ‘cost’ for - control of both systemic and CNS infection.