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CSF concentrations of soluble TREM2 as a marker of microglial activation in HIV-1 infection

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Abstract

Objective
To explore changes in CSF sTREM2 concentrations in the evolving course of HIV-1 infection.

Methods
In this retrospective cross-sectional study, we measured concentrations of the macrophage/microglial activation marker sTREM2 in CSF samples from 121 HIV-1–infected adults and 11 HIV-negative controls and examined their correlations with other CSF and blood biomarkers of infection, inflammation, and neuronal injury.

Results
CSF sTREM2 increased with systemic and CNS HIV-1 disease severity, with the highest levels found in patients with HIV-associated dementia (HAD). In untreated HIV-1–infected patients without an HAD diagnosis, levels of CSF sTREM2 increased with decreasing $CD4^+$ T-cell counts. CSF concentrations of both sTREM2 and the neuronal injury marker neurofilament light protein (NFL) were significantly associated with age. CSF sTREM2 levels were also independently correlated with CSF NFL. Notably, this association was also observed in HIV-negative controls with normal CSF NFL. HIV-infected patients on suppressive antiretroviral treatment had CSF sTREM2 levels comparable to healthy controls.

Conclusions
Elevations in CSF sTREM2 levels, an indicator of macrophage/microglial activation, are a common feature of untreated HIV-1 infection that increases with $CD4^+$ T-cell loss and reaches highest levels in HAD. The strong and independent association between CSF sTREM2 and CSF NFL suggests a linkage between microglial activation and neuronal injury in HIV-1 infection. CSF sTREM2 has the potential of being a useful biomarker of innate CNS immune activation in different stages of untreated and treated HIV-1 infection.

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Glossary

HAD = HIV-associated dementia; **HAND** = HIV-associated neurocognitive disorder; **IFN** = interferon; **MSD** = Meso Scale Discovery; **NA** = neuroasymptomatic; **NFL** = neurofilament light protein; **WBC** = white blood cell.

Despite expressing low levels of CD4,[1,2] microglia and perivascular macrophages in the CNS are important targets of HIV-1 infection and likely key mediators of neuropathic inflammation and neuronal injury in HIV-1 infection, particularly during its advanced phase. Microglia are the resident myeloid cells in the CNS and are important components of the local innate immune response to HIV-1 and may be critical in the chronic immune activation characteristic of CNS in untreated HIV-1.[3] The chronic activation of microglia and macrophages in HIV-1 together with possible microglial dysfunction[4] are probably involved in the pathogenesis of HIV-associated neurocognitive disorders (HANDs) and HIV-associated dementia (HAD).[5]

TREM2 is a receptor glycoprotein that belongs to the immunoglobulin superfamily. In the brain, TREM2 is expressed exclusively by myeloid cells, including microglia and macrophages.[6] In vitro, TREM2 promotes phagocytosis, suppresses Toll-like receptor-induced inflammatory cytokine production, and enhances anti-inflammatory cytokine transcription.[7] Its expression in the brain is upregulated in response to the tissue damage that accumulates in aging and in neurodegenerative diseases.[8] Increased CSF concentrations of soluble TREM2 (sTREM2) have been noted in Alzheimer disease[9,10] and MS.[11,12]

The aim of this study was to explore changes in CSF sTREM2 through different stages of untreated and treated HIV-1 infection and to examine the relation of this microglial and macrophage activation marker to changes in other markers of inflammation and neuronal injury across a broad spectrum of HIV-1 infection.

Methods

Study design and patients

Archived blood and CSF samples from 121 HIV-infected adults and 11 HIV-negative controls from Gothenburg, Sweden, and San Francisco, CA, were analyzed in this retrospective cross-sectional study. All samples were collected between 1999 and 2014 within the context of research protocols. Selection of samples was performed to obtain a distribution of groups representing progression of systemic HIV and the presentation of overt neurologic disease and was not intended to reflect the prevalence of treatment, systemic or CNS disease severity, or treatment in the study sites.[13] All participants were clinically evaluated for neurologic and neurocognitive symptoms, but formal neurocognitive testing was not routinely performed. Participants were grouped as outlined in previous studies[14,15]: 4 groups of chronically HIV-infected patients without overt neurologic complaints or signs, designated as "neuroasymptomatic" (NA) and divided by blood $CD4^+$ T-cell counts into 4 groups with >350, 200–349, 50–199, and CD4 < 50 cells/μL. The group presenting with HAD was defined in accordance with the Centers for Disease Control and Prevention and the American Academy of Neurology Task force criteria.[16,17] All these participants were either antiretroviral treatment (ART) naive or off treatment for at least 6 months when sampled. We also included a group of treated HIV-infected patients with plasma HIV RNA suppression to below 50 copies/mL for >1 year (ART suppressed). A group of uninfected (HIV-negative) healthy controls (n = 11) were included for comparison.

Standard protocol approvals and patient consents

This study was approved by the institutional review boards of the 2 study sites. All blood and CSF samples were analyzed after obtaining informed consent of participants under these institutional review board-approved protocols. If their capacity to provide consent was questioned, consent was also obtained from those with power of attorney.

Blood and CSF sampling

Blood and CSF were obtained according to standard protocols as previously described.[18,19] CSF was immediately centrifuged at low speed to remove cells and thereafter aliquoted and stored within 1 hour of collection at ≤−70°C until the time of the biomarker assays. Blood was collected in EDTA tubes, and plasma was aliquoted and stored in parallel with CSF for later batch assays.

Laboratory methods

CSF sTREM2 was measured using an in-house electrochemiluminescence assay on a Meso Scale Discovery (MSD) SECTOR imager 6000 (MSD, Rockville, MD), using a method adapted from Kleinberger et al.[20] The capture antibody was biotinylated polyclonal goat anti-human TREM2 (0.25 μg/mL R&D Systems, Minneapolis, MN), and the detector antibody was monoclonal mouse anti-human TREM2 (1 μg/Ml Santa Cruz Biotechnology, Dallas, TX). A standard curve for calculations of unknowns was constructed using recombinant human TREM2 (4,000–62.5 pg/mL), and CSF samples were diluted 1:4 before being assayed. For a more comprehensive description of the method, please see Alosco et al.[21] Intra-assay coefficients of variability were <15%, and all samples were measured on the same day using the same reagents.

Neopterin concentrations were analyzed in serum and CSF by a commercially available immunoassay (BRAHMS, Hennigsdorf, Germany), with an upper normal reference value of 8.8 nmol/L in blood and 5.8 nmol/L in CSF.[22]

CSF neurofilament light protein (NFL) concentrations were measured by means of a sensitive sandwich assay (NF-light ELISA kit; UmanDiagnostics AB, Umeå, Sweden) as previously described.[15,23] CSF NFL was age adjusted to the study population median of 42 years when comparing CSF NFL in different study groups. The upper limit of normal was <773 ng/L, based on the antilog of the log scale mean + 2 SD in 359 healthy controls.[24]

The Cobas TaqMan RealTime HIV-1 (version 1 or 2; Hoffmann-La Roche, Basel, Switzerland) and the Abbott RealTime HIV-1 assay (Abbot Laboratories, Abbot Park, IL) were used to measure HIV RNA levels in cell-free CSF and plasma at each site. The study visits included assessments of CSF white blood cell (WBC) count, CSF and blood albumin, and blood $CD4^+$ and $CD8^+$ T lymphocyte counts by local clinical laboratories using routine methods.

Statistical methods

Descriptive statistics were performed using Prism (version 7; Graphpad Software Inc, La Jolla, CA) or SPSS (IBM SPSS version 22) software. Continuous variables were $\log_{10}$ transformed where appropriate to reduce skewness. Comparison of biomarker concentrations was performed with one-way analysis of variance and Tukey multiple comparison tests for evaluation of multiple groups. Biomarker associations were analyzed with Pearson correlation analysis. The relationship between age $\log_{10}$ CSF sTREM2, NFL, and neopterin levels, were analyzed with linear regression.

Data availability

The data sets analyzed during the current study are available from the corresponding author on reasonable request.

Results

A total of 121 HIV-1–infected patients (49 women and 72 men) and 11 HIV-negative controls (4 women and 7 men) were studied. Eighty-five of the included HIV-1–infected patients were untreated and NA: 25 with $CD4^+$ >350, 20 with $CD4^+$ 200–349, 20 with $CD4^+$ 50–199, and 21 with $CD4^+$ T-cell count <50 cells/μL; 7 additional untreated patients had HAD (at the time categorized as AIDS dementia complex using Memorial Sloan-Kettering Stage[25] 1, n = 4; stage 2, n = 2; and stage 3, n = 1); 28 patients were on suppressive stable ART. The background clinical, laboratory, and demographic data for each subject group are summarized in table 1.

Overall, the comparison of subgroups showed a significant difference in CSF sTREM2 concentrations between the groups ($p < 0.001$). The highest CSF sTREM2 levels were found in patients with HAD, followed by untreated NA patients with low $CD4^+$ T-cell counts (figure 1, A). HIV-infected patients on suppressive antiretroviral treatment had CSF sTREM2 levels comparable to healthy controls. The group with high $CD4^+$ T-cell counts (>350 cells/μL) had the lowest CSF sTREM2 concentrations among untreated NA patients, and CSF sTREM2 increased gradually in groups with lower blood $CD4^+$ T-cell counts. Consequently, a reverse correlation was found between CSF sTREM2 and $CD4^+$ T-cell count in NA patients ($r = -0.32$, $p < 0.01$). Similar differences between the groups were also found in CSF neopterin (figure 1, B) and CSF NFL (figure 1, C). Statistical outcomes of group comparisons in these 3 biomarkers are shown in table 2.

CSF sTREM2 showed a significant correlation with CSF neopterin ($r = 0.45$, $p < 0.0001$) and CSF NFL ($r = 0.62$, $p < 0.0001$) in the full cohort. A correlation was also found between CSF neopterin and CSF NFL ($r = 0.50$, $p < 0.0001$), figure 2, A–C. Figure e-1 (links.lww.com/NXI/A81) shows a heat map of the Pearson correlation analysis that provides a visual overview of the biomarker associations.

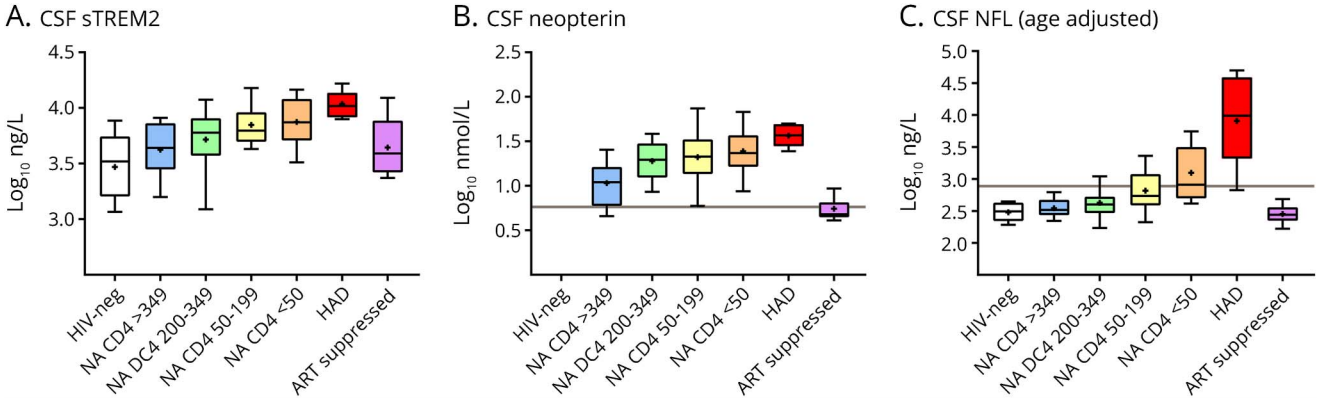
Age, CSF neopterin, and albumin ratio stood out as independent predictors of CSF sTREM2 in a multivariable

Table 1 Background characteristics

		Age	Plasma HIV RNA	CSF HIV RNA	Blood $CD4^+$ T cells
Groups	**N**	**Median years (IQR)**	**Median Log_{10} (IQR)**	**Median Log_{10} (IQR)**	**Median cells/mL (IQR)**
HIV negative	11	39 (29–53)	NA	NA	ND
Neuroasymtpomatic HIV (NA)					
CD4 > 350	25	40 (30–47)	4.12 (3.54–4.64)	3.43 (2.41–4.13)	480 (395–705)
CD4 200–349	20	38 (31–45)	4.76 (4.32–5.31)	4.10 (3.44–4.52)	240 (212–285)
CD4 50–199	20	36 (32–50)	5.28 (4.65–5.64)	4.32 (3.77–4.91)	105 (62–148)
CD4 < 50	21	44 (35–48)	5.60 (5.08–5.90)	3.25 (2.13–3.76)	15 (10–30)
HAD	7	43 (42–62)	5.76 (5.23–5.96)	4.98 (4.14–5.45)	54 (31–80)
HIV, treated-suppressed (ART suppressed)	28	45 (34–58)	<1.30 (<1.30–<1.30)	<1.30 (<1.30–<1.30)	595 (452–862)

Abbreviations: HAD = HIV-associated dementia; IQR = interquartile range; NA = neuroasymtpomatic.

Figure 1 Concentrations of CSF biomarkers in the 7 participant groups



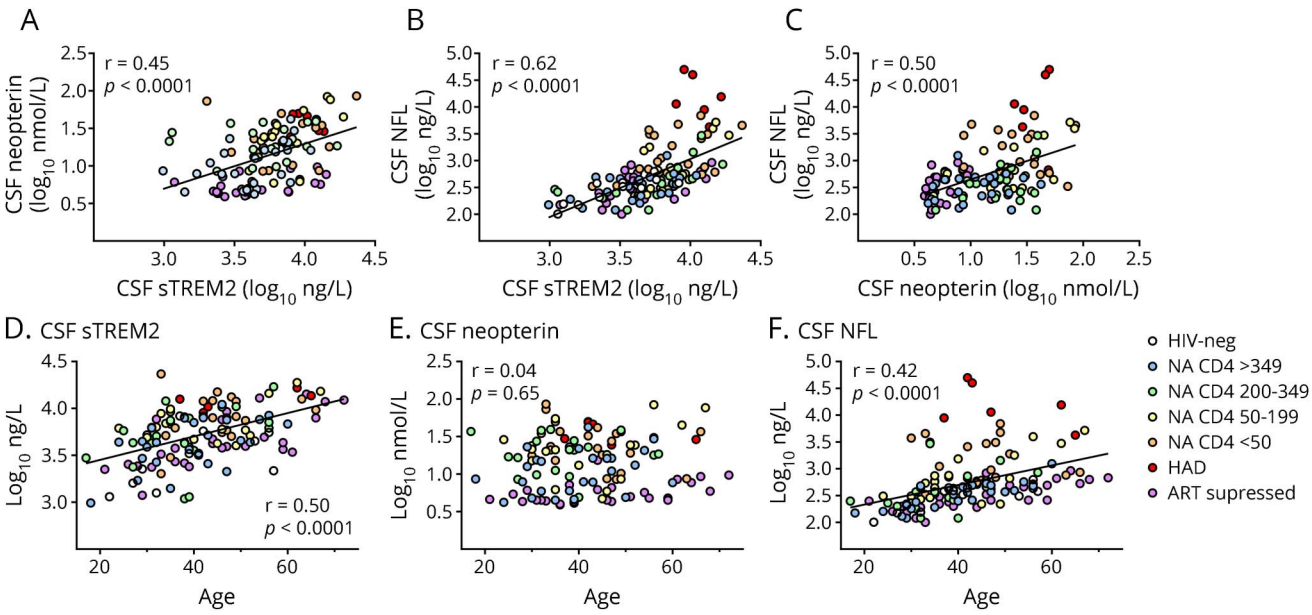
The figure shows concentrations of CSF sTREM2 (A), CSF neopterin (B), and age-adjusted CSF NFL (C) in the 7 participant groups. Boxes in all panels depict median and IQR, whiskers show 10–90 percentiles, and "+" designates the mean values. Gray horizontal lines show the upper limit of normal. Statistical comparisons of groups are given in table 2. Measured markers are listed in the title of each panel and findings described in the text.

Table 2 Comparisons of CSF sTREM2, neopterin, and NFL concentrations among groups

Group comparisons	CSF sTREM2 (log)	CSF Neopterin (log)	CSF NFL (log)
	Overall ANOVA *p*		
	<0.001	<0.001	<0.001
	Tukey multiple comparison		
HAD vs HIV−	<0.001	a	<0.001
HAD vs NA CD4 ≥ 350	<0.01	<0.001	<0.001
HAD vs NA CD4 200–349	ns	ns	<0.001
HAD vs NA CD4 50–199	ns	ns	<0.001
HAD vs NA CD4 < 50	ns	ns	<0.001
HAD vs ART suppressed	<0.01	<0.001	<0.001
NA CD4 < 50 vs HIV−	<0.01	a	<0.001
NA CD4 < 50 vs NA CD4 ≥ 350	<0.05	<0.001	<0.001
NA CD4 < 50 vs NA CD4 200–349	ns	ns	<0.001
NA CD4 < 50 vs NA CD4 50–199	ns	ns	ns
NA CD4 < 50 vs ART suppressed	<0.05	<0.001	<0.001
NA CD4 50–199 vs HIV−	<0.05	a	ns
NA CD4 50–199 vs NA CD4 ≥ 350	ns	<0.01	ns
NA CD4 50–199 vs ART suppressed	ns	<0.001	<0.01
NA CD4 200–349 vs NA CD4 ≥ 350	ns	<0.05	ns
NA CD4 200–349 vs ART suppressed	ns	<0.001	ns
NA CD4 ≥ 350 vs ART suppressed	ns	<0.01	ns

Abbreviations: ANOVA = analysis of variance; HAD = HIV-associated dementia; NA = neuroasymtpomatic; NFL = neurofilament light protein; ns = not significant.
[a] CSF neopterin missing on HIV-negative participants.

Figure 2 Correlations between CSF biomarkers and age



The figure shows correlations between CSF sTREM2, neopterin, and NFL (A–C). Regression lines and Pearson correlation coefficient are shown in each panel. Associations between CSF biomarkers and age (D–F). Regression lines and Pearson correlation coefficient are shown in panel D and F. No significant correlation was found between CSF neopterin and age (E). NFL = neurofilament light protein.

analysis, including patients from all HIV groups, that included CSF sTREM2 vs age, blood $CD4^+$ T-cell count, CSF WBC, albumin ratio, plasma and CSF HIV RNA, serum and CSF neopterin, and ART (table 3).

CSF sTREM2 was confirmed as an independent predictor of CSF NFL together with age, $CD4^+$ T-cell count, and CSF HIV RNA in a multiple linear regression analysis (table 3).

CSF sTREM2 and age

CSF sTREM2 and CSF NFL increased significantly with age while no correlation between age and CSF neopterin was found (figure 2, D–F).

When the 11 HIV-negative controls were exclusively evaluated, a very strong correlation was found between CSF sTREM2 and CSF NFL ($r = 0.85$, $p < 0.01$; figure 3, A), although CSF NFL was within the normal range in all 11 controls. Both these CSF biomarkers increased with normal aging (figure 3, B). Age and CSF sTREM2 stood out as independent predictors of CSF NFL in a multivariable analysis (not shown). To be noted, neither $CD4^+$ T cells nor neopterin levels were available in the group of healthy controls.

Discussion

In this study, we found that CSF concentrations of sTREM2 increased with systemic HIV-1 disease progression as indicated by blood $CD4^+$ T-cell loss. High CSF sTREM2 levels were generally found in patients with HAD. Microglia and perivascular macrophages are important target cells for HIV-1 in the brain. In addition, these cells are also mediators of inflammatory processes that may cause neuronal dysfunction and injury as results of their activation. Microglial activation is characteristic of and consistently found in HIV-1 encephalitis.[26]

We also found that CSF sTREM2 levels were strongly correlated with CSF concentrations of NFL. CSF NFL is typically markedly increased in HAD[15] reflecting ongoing axonal injury, something that was found also in the present study (table e-1, links.lww.com/NXI/A82). However, compared with nondemented patients with correspondingly high CSF sTREM2 concentrations, patients with HAD had considerably higher CSF NFL. A similar pattern was also found for CSF neopterin. This may suggest that macrophage and microglial activation is not enough to cause neurodegeneration in HAD but that also other mechanisms than immune activation probably are involved in the pathogenesis.

ART has had a profound effect on morbidity and mortality of HIV-1 infection, including HAD and other complications involving the CNS.[27] However, while substantially reduced by ART, residual CNS immune activation has been found in almost half of the patients with durably suppressed plasma and CSF virus.[28] In the present study, 36% of patients on suppressive ART still had CSF neopterin levels above the upper normal reference limit. However, no significant difference in CSF sTREM2 between ART-treated HIV-1–infected patients and HIV-negative controls was found in this study. This may suggest that the persistent CNS immune activation that is commonly

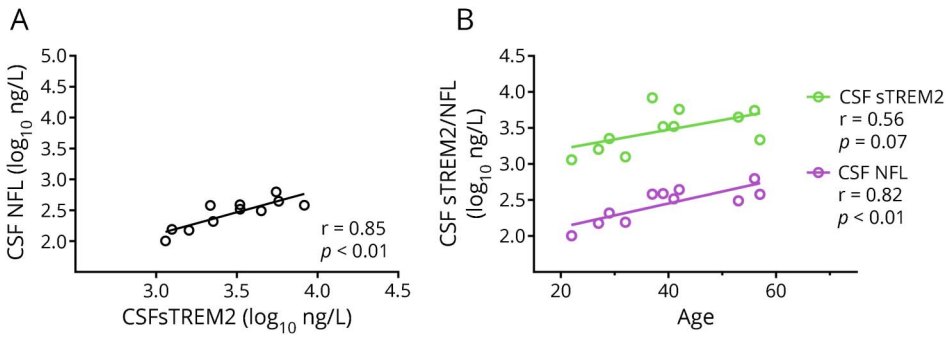
Table 3 Univariable correlation (left columns) and multiple linear regression (right columns) determining predictors of log_{10} CSF sTREM2 and log_{10} CSF NFL

	Univariable		Multivariable	
Predictor	**Std b (*r*)**	***p***	**Std b_{adj}**	***p***
Predicting CSF sTREM2				
Age	0.504	<0.001	0.384	<0.001
CD4	−0.356	<0.001		
CSF WBC	0.008	0.931		
CSF/P albumin ratio	0.492	<0.001	0.297	<0.001
P HIV RNA	0.344	<0.001		
CSF HIV RNA	0.295	0.001		
S neopterin	0.409	<0.001		
CSF neopterin	0.454	<0.001	0.385	<0.001
ART	−0.204	0.024		
Predicting CSF NFL				
Age	0.406	<0.001	0.300	0.001
CD4	−0.536	<0.001	−0.384	<0.001
CSF WBC	−0.064	0.489		
CSF/P albumin ratio	0.413	<0.001		
CSF HIV RNA	0.351	<0.001	0.184	0.017
CSF neopterin	0.498	<0.001		
CSF sTREM2	0.897	<0.001	0.258	0.003
ART	−0.276	0.002		

Abbreviations: NFL = neurofilament light protein; WBC = white blood cell.

found in patients on effective ART is not mainly driven by macrophage/microglial activation, but rather by activated lymphocytes or astrocytes. The pteridine metabolite neopterin has been extensively studied in HIV. Increased CSF levels are generally found in untreated HIV[22] and can also, as previously mentioned, often be found in patients on ART[5,28] and are slightly higher in ART-treated non-HAD patients with milder forms of HAND compared with unimpaired patients.[5] Neopterin is produced primarily in monocytes/macrophages and related cells, and the most important stimuli are interferons

Figure 3 CSF sTREM2 in HIV-negative controls



(A) A strong correlation between CSF sTREM2 and CSF NFL was found in HIV-negative controls (n = 11). (B) Both CSF sTREM2 and NFL increase with age in healthy controls. NFL = neurofilament light protein.

(IFNs), especially Th1-type cytokine IFN-γ.[29] However, astrocytes can also produce neopterin on activation,[30] and CSF concentrations of neopterin can probably increase also during lymphocytic inflammation, as seen in, for example, early HIV-1 infection with aseptic meningitis.

TREM2 is an innate immune receptor expressed exclusively on the surface of cells of the monocytic lineage. It is a type-1 transmembrane glycoprotein with an ectodomain that is proteolytically cleaved and released into the extracellular space as a soluble variant (sTREM2), making sTREM2 a more specific biomarker of macrophage/microglial activity than neopterin. The process whereby sTREM2 is released into the extracellular space and the CSF is also different compared with the mechanisms that are driving neopterin production, which may contribute to different expressions of these 2 biomarkers. CSF sTREM2 may be a later and therefore less sensitive marker of macrophage/microglial activation than neopterin, thereby requiring larger numbers of study participants to disclose possible differences between the groups, an assumption that may be supported by the fact that we could not demonstrate any difference between HIV negatives and ART-treated study participants in CSF NFL either, although a small but significant difference has been found in previous larger studies.[15,31] CSF neopterin was not available in HIV-negative controls in the present study.

Brain imaging using PET has been studied as an in vivo method to reveal microglial activation,[32,33] but it may not be sensitive enough in HIV, at least when the translocator protein (TSPO) ligand is used.[34] PET scanning is also expensive and not generally available, and it would be beneficial to identify a reliable CSF biomarker of macrophage/microglial activation in HIV. Such a marker could facilitate studies exploring pathogenesis of neuro-HIV in untreated and treated HIV-infected patients and potentially also employ a clinical usage in treated patients with cognitive impairment.

Other markers of microglial activation that have been suggested for studies in HIV are sCD163, sCD14, Monocyte chemoattractant protein-1 (MCP-1), Chitinase-3-like protein 1 (YKL-40), and ganglioside GD3.[3,35–38] However, most of those are not sufficiently specific for microglial and macrophage activation. sTREM2, the secreted form of the triggering receptor, is exclusively expressed on myeloid cells but not on astrocytes and therefore has the potential to become a CSF biomarker selective for macrophage/microglial activation.

Of interests, a strong correlation between CSF sTREM2 and CSF NFL levels was also found in HIV-negative controls with normal CSF NFL in relation to their age. The brain displays an increasing inflammatory state with aging, and both microglial dysfunction and neuronal injury increase with normal aging.[39] Age-related microglial activation coincides with age-related neurodegeneration and cognitive decline,[40] and the results from our small cohort of HIV-negative controls support a linkage between microglial activation and axonal injury in normal aging. This is a research area of great interest that needs to be further explored.

This study has several limitations. Although the total number of participants was reasonably large, some of the groups were limited in size, especially the HAD group because of its low incidence. We used a cross-sectional design to reconstruct a longitudinal process. It has become increasingly difficult to perform longitudinal studies on untreated patients when early and universal ART is standard. Neurocognitive performance testing was not consistently performed in non-HAD patients, precluding examination of associations of CSF sTREM2 level elevations with milder forms of HAND. Although TREM2 is exclusively expressed by myeloid cells, CSF sTREM2 levels cannot distinguish between microglial and macrophage activation. The various contributions of these cells to the CNS immune activation and pathogenesis in HIV-1 disease have not been established and also cannot be determined by the results of this study.

Macrophage/microglial activation, as measured by CSF sTREM2, increased with decreasing $CD4^+$ T-cell counts in NA HIV and was especially high in HAD. The magnitude of the increase in CSF sTREM2 levels in HAD relative to healthy controls was similar to that previously noted in Alzheimer disease and MS.[10,12] Both CSF sTREM2 and CSF NFL increase with normal aging, but there is also a strong independent association between CSF sTREM2 and axonal injury as measured by CSF NFL. Of interest, this is also the case in healthy controls. Our results suggest that CSF sTREM2 is a potentially useful biomarker of microglial activation in different stages of HIV infection.

Author contributions

M. Gisslén and H. Zetterberg originated the idea and supervised the study. M. Gisslén, A. Yilmaz, L.-M. Andersson, L. Hagberg, S. Spudich, and R.W. Price recruited the participants and were responsible for the initial cohort study design. A. Heslegrave, E. Veleva, D. Fuchs, and H. Zetterberg performed the biochemical analyses. A. Yilmaz, L.-M. Andersson, L. Hagberg, S. Spudich, and R.W. Price contributed to the acquisition, analysis, and interpretation of data. M. Gisslén performed the statistical analyses and oversaw the preparation of this report. All the authors contributed to the manuscript preparation.

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Disclosure

M. Gisslen served on the scientific advisory board of Gilead, BMS, Janssen, and MSD; received speaker honoraria from

Gilead, BMS, and Janssen; served as editor of *HIV & Virology News*; served on the editorial board of *AIDS Research and Therapy*; and received research support from Gilead and Janssen. A. Heslegrave, E. Veleva, A. Yilmaz, and L.-M. Andersson report no disclosures. L. Hagberg served as an associate editor of *Infectious Diseases*. S. Spudich served as a guest editor of *Seminars in Neurology*; served as section editor of *Current HIV/AIDS Reports*; served on the editorial board of the *Journal of Virus Eradication*; served as guest editor of *AIDS*; and received research support from ViiV Healthcare and the NIH. D. Fuchs served as chief editor of *Pteridines*. R.W. Price received publishing royalties from Wolters Kluwer Health and received research support from the NIDA, NIMH, NIMH/NIAID, NINDS, and NIAID/NIMH. H. Zetterberg served on the scientific advisory boards of Roche and Eli Lilly; served as an associate editor of the *Journal of Alzheimer's Disease* and *Alzheimer's & Dementia*; served as editor of *Molecular and Cellular Neuroscience and Scandinavian Journal of Clinical and Laboratory Investigation*; is cofounder of Brain Biomarker Solutions; and received research support from Swedish State Support for Clinical Research, Knut, and Alice Wallenberg Foundation. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

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