Supplemental text part I:

The following neuropsychological tests were used: 1)Trailmaking Part A (processing speed); 2)Trailmaking Part B (executive function); 3)Hopkins Verbal Learning Test-Revised (HVLT-R) total recall (verbal learning); 4) HVLT delayed recall (verbal memory); 5) Grooved Pegboard dominant hand (fine motor); 6) Grooved Pegboard non-dominant hand (fine motor); 7) Stroop Color Naming (processing speed) 8) Stroop Color/Word (executive function); and 9) Controlled Oral Word Association Test (verbal fluency). Raw scores on these tests were converted to mean T scores based on published demographic norms with mean= 50 and standard deviation= 10.[1-4]. Global Deficit Score (GDS), a validated measure of neurocognitive impairment in HIV based on T scores was also calculated.[5] GDS-9 $\geq$ 0.5 is consistent with overall impairment.

Supplemental text part II:

We conducted a series of linear regression analyses to examine the baseline relationship between NPT-9 and each CSF/plasma biomarker in PWH. A baseline association between NPT-9 and CSF and plasma HIV RNA was also assessed. We also performed models adjusting for either CSF or plasma HIV RNA. These regression analyses were repeated with CSF NFL as the dependent variable to evaluate the baseline relationship between neuronal damage and CSF/plasma levels of inflammation. Likewise, to examine the demographic-adjusted relationship between neuronal damage and inflammation in PWOH, separate linear regression analyses were performed with CSF NFL as the dependent variable and each one of the CSF/plasma biomarkers as the independent variable. We applied a natural log transformation to CSF NFL values to correct for a right skew and calculated exponentiated coefficients, from which we subtract 1 and multiply by 100 to obtain the expected percent change in CSF NFL, given unit increase in the

independent variable. All models for this analysis were adjusted for age, gender and race as covariates.

To account for potential confounding effects on the NPT-9 and CSF NFL outcomes, we simultaneously considered all CSF/plasma biomarkers and demographic variables in the same linear regression model. When correlated biomarkers are included in the same model, regression coefficient estimates can be unstable. Although automated model selection procedures such as Stepwise and LASSO can address this issue,[6] they suffer from two fundamental drawbacks: a) they tend to randomly pick only one or few of highly correlated biomarkers that are related to some extent to the outcome;[7] and b) they do not account for model selection uncertainty based on a single sample, often tending to reject null hypotheses more often than the nominal levels would suggest, and to produce confidence intervals that are too narrow.[8] The latter problem of overly liberal inference persists in other sophisticated model selection methods including Elastic Net [7] and Least Angle Regression.[9]

Therefore, to formally account for uncertainty in model selection, we applied a Bayesian Model Averaging (BMA) method.[10] BMA considers all possible multiple linear models that can be formed using candidate predictors, and performs robust estimation and inference that are averaged over all these models. Our data included 13 covariates for PWH (age, race, gender, CSF/Plasma MCP-1, CSF/plasma neopterin, CSF/plasma TNFα, CSF/Plasma sCD14 and CSF/plasma HIV RNA) and 9 covariates for PWOH (all as above, except CSF/Plasma sCD14 and CSF/plasma HIV RNA); that is, all 2^{13} and 2^{9} possible models are respectively considered. Let β denote a regression coefficient of a particular covariate in a given linear model. Three measures are of main interest. First, a Bayesian point estimate of β is its posterior mean, E[β|Data], which, under the BMA framework, represents the weighted average of the model-

specific point estimates of the coefficient across every possible model configuration. Herein, the coefficient estimate in a more plausible model according to our data receives more weight. Second, SD[β|Data] denotes a posterior standard deviation of β under the BMA framework. Third, P(β≠0 |Data) is a posterior probability that β equals zero, that is, the posterior probability of the corresponding covariate being a risk factor of outcome. We call this the posterior effect probability (PEP) and use it for Bayesian hypothesis testing, If PEP < 0.5, there is no evidence for the covariate being a risk factor; if 0.5 ≤ PEP < 0.75, there is weak evidence; if 0.75 ≤ PEP < 0.95 there is a positive evidence; if 0.95 ≤ PEP ≤1, there is strong evidence.[11]

Our next statistical analyses focused on longitudinal measurements of CSF/plasma biomarkers collected at the two sequential visits in both PWH and PWOH. We initially performed a paired Wilcoxon signed-rank test to evaluate change in each of CSF/plasma between the two visits in each group. We then used a series of separate linear regression models to determine whether a decrease in each biomarker independently predicted an improvement in NPT-9 or CSF NFL over time. Similarly, we also used a series of separate linear regression models to determine whether baseline biomarker values independently predicted an improvement in NPT-9 or CSF NFL over time. All models were adjusted for age, sex, and race/ethnicity. To account for potential confounding on each outcome, we simultaneously considered all CSF/plasma biomarkers and clinical variables in a single linear model, and applied BMA to account for model selection uncertainty and perform robust estimation and inference. For CSF NFL, we considered a difference in natural log-transformed values between the two visits (i.e., loge CSF NFL at second visit – loge CSF NFL at baseline) due to left skewness of the distribution of raw differences. Exponentiated coefficients, from which we subtract 1 and multiply 100, were calculated to obtain the expected percent change in the ratio of the CSF NFL

measurement at second visit to that at the first visit, given unit increase in the independent variable.

All statistical analyses except for BMA were carried out using SAS software version 9.4 (SAS Institute Inc, Cary, NC). Assumptions of linear regression were checked (linearity, normality of residuals and homoscedasticity). For the purposes of regression, Cook's distance was used to identify outliers with inordinate effects on the models. One outlier with abnormally high CSF sCD14 value (with Cook's distance of >20) was removed for the regression analysis. Additionally, there was 1 missing CSF NFL value and one missing CSF neopterin value from the PWOH group at baseline. These visits were removed for the purposes of regression, leaving 54 PWOH at baseline for regression analysis. All tests were two-sided with significance level of 0.05. BMA was conducted using R package "BMS" in R version 3.6.1 (R Core Team 2019).

References

1. Diehr MC, Cherner M, Wolfson TJ, et al. The 50 and 100-item short forms of the Paced Auditory Serial Addition Task (PASAT): demographically corrected norms and comparisons with the full PASAT in normal and clinical samples. Journal of clinical and experimental neuropsychology 2003;25:571-85.
2. Heaton R, Taylor M, Manly J. Demographic effects and use of demographically corrected norms with the WAIS-III and WMS-III. Clinical Interpretation of the WAIS-III and WMS-III. San Diego, CA: Academic Press, 2002.
3. Heaton RK, Miller SW, Taylor MJ, Grant I. Revised Comprehensive norms for an expanded Halstead- Reitan Battery: Demographically adjusted neuropsycho- logical norms for African American and Caucasian adults scoring program Lutz, FL.: Psychological Assessment Resources; 2004.
4. Norman MA, Moore DJ, Taylor M, et al. Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-Card Version. Journal of clinical and experimental neuropsychology 2011;33:793-804.
5. Carey CL, Woods SP, Gonzalez R, et al. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. Journal of clinical and experimental neuropsychology 2004;26:307-19.
6. Tibshirani R. Regression shrinkage and selection via the Lasso. J Roy Stat Soc B Met 1996;58:267-88.
7. Zou HH, H. Regularization and variable selection via the elastic net. J R Stat Soc Series B Stat Methodol 2005;67:301-20.
8. Chatfield C. Model uncertainty, data mining and statistical inference. J R Stat Soc Ser A Stat Soc 195;158:419–66.
9. Efron BH, T.; Johnstone, I.; Tibishirani, R. Least Angle Regression. Ann Stat 2004;32:407-99.
10. Hoeting JM, D.; Raftery, A.; Volinsky, C. Bayesian Model Averaging: A Tutorial. Statistical Science 1999;14:382-417.
11. Viallefont V, Raftery AE, Richardson S. Variable selection and Bayesian model averaging in case-control studies. Stat Med 2001;20:3215-30.

Supplemental Table A: Linear regression analyses for associations between NPT-9 and each one of the CSF/Plasma biomarkers at baseline in HIV+ participants (n=52 except for CSF sCD14 for which n=51)

Biomarker	Unit	β (SE)	[95% CI]	P-value
CSF and Plasma HIV RNA as separate predictors				
CSF MCP-1	Per 1,000 pg/ml increase	-2.34 (0.59)	[-3.52, -1.17]	< **0.001**
Plasma MCP-1	Per 1,000 pg/ml increase	-7.41 (5.36)	[-18.20, 3.38]	0.174
CSF Neopterin	Per 10 nmol/l increase	-1.71 (0.61)	[-2.93, -0.49]	**0.007**
Plasma Neopterin	Per 10 nmol/l increase	-1.62 (0.55)	[-2.74, -0.51]	**0.005**
CSF TNFα	Per 10 pg/ml increase	-0.57 (2.07)	[-4.73, 3.60]	0.785
Plasma TNFα	Per 10 pg/ml increase	-0.63 (0.57)	[-1.78, 0.52]	0.274
CSF sCD14	Per 100,000 pg/ml increase	-3.65 (1.91)	[-7.50, 0.20]	0.062
Plasma sCD14	Per 100,000 pg/ml increase	-0.65 (0.19)	[-1.03, -0.26]	**0.002**
CSF HIV RNA	Per 10-fold increase	-1.14 (1.14)	[-3.43, 1.15]	0.322
Plasma HIV RNA	Per 10-fold increase	-3.02 (1.30)	[-5.64, -0.39]	**0.025**
Adjusting for plasma HIV RNA				
CSF MCP-1	Per 1,000 pg/ml increase	-2.08 (0.61)	[-3.31, -0.85]	**0.001**
Plasma MCP-1	Per 1,000 pg/ml increase	-6.66 (5.16)	[-17.05, 3.72]	0.203
CSF Neopterin	Per 10 nmol/l increase	-1.34 (0.66)	[-2.68, -0.01]	**0.049**
Plasma Neopterin	Per 10 nmol/l increase	-1.38 (0.56)	[-2.51, -0.26]	**0.017**
CSF TNFα	Per 10 pg/ml increase	-0.37 (1.99)	[-4.36, 3.63]	0.854
Plasma TNFα	Per 10 pg/ml increase	-0.78 (0.54)	[-1.87, 0.32]	0.159
CSF sCD14	Per 100,000 pg/ml increase	-2.96 (1.89)	[-6.78, 0.85]	0.125
Plasma sCD14	Per 100,000 pg/ml increase	-0.59 (0.19)	[-0.97, -0.21]	**0.003**
Adjusting for CSF HIV RNA				
CSF MCP-1	Per 1,000 pg/ml increase	-2.40 (0.63)	[-3.67, -1.13]	**< 0.001**
Plasma MCP-1	Per 1,000 pg/ml increase	-7.39 (5.36)	[-18.19, 3.40]	0.175
CSF Neopterin	Per 10 nmol/l increase	-2.66 (0.88)	[-4.43, -0.89]	**0.004**
Plasma Neopterin	Per 10 nmol/l increase	-1.58 (0.58)	[-2.75, -0.40]	**0.010**
CSF TNFα	Per 10 pg/ml increase	1.19 (2.66)	[-4.16, 6.55]	0.656
Plasma TNFα	Per 10 pg/ml increase	-0.54 (0.58)	[-1.71, 0.63]	0.360
CSF sCD14	Per 100,000 pg/ml increase	-4.07 (2.24)	[-8.58, 0.45]	0.076
Plasma sCD14	Per 100,000 pg/ml increase	-0.63 (0.20)	[-1.03, -0.23]	**0.003**

Significant P values (<0.05) are in bold font.
Abbreviations: NPT = Neuropsychological summary T score; SE = Standard error; CI = confidence interval; pg = picograms; ml = milliliter; nmol = nanomole
All models are adjusted for age, race, and gender.

Supplemental Table B: Linear regression analyses for assessing association between CSF NFL (natural log transformed) and each one of the CSF/plasma biomarkers at baseline in HIV+ (n=52 except for CSF sCD14 for which n=51) and HIVnegative participants (n=55 except for CSF neopterin for which n=54).

Biomarker	Unit	β (SE)	e^{β} [95% CI]	P-value
CSF and Plasma HIV RNA as separate predictors for HIV+ participants				
CSF MCP-1	Per 1,000 pg/ml increase	0.321 (0.071)	1.379 [1.196, 1.589]	**< 0.001**
Plasma MCP-1	Per 1,000 pg/ml increase	-0.730 (0.675)	0.482 [0.124, 1.875]	0.285
CSF Neopterin	Per 10 nmol/l increase	0.406 (0.057)	1.501 [1.339, 1.683]	**< 0.001**
Plasma Neopterin	Per 10 nmol/l increase	0.140 (0.073)	1.150 [0.994, 1.330]	0.060
CSF TNFα	Per 10 pg/ml increase	0.848 (0.228)	2.334 [1.477, 3.689]	**< 0.001**
Plasma TNFα	Per 10 pg/ml increase	0.071 (0.071)	1.074 [0.930, 1.239]	0.325
CSF sCD14	Per 10,000 pg/ml increase	0.109 (0.021)	1.115 [1.069, 1.163]	**< 0.001**
Plasma sCD14	Per 100,000 pg/ml increase	0.041 (0.026)	1.042 [0.989, 1.098]	0.119
CSF HIV RNA	Per 10-fold increase	0.499 (0.124)	1.647 [1.283, 2.114]	**< 0.001**
Plasma HIV RNA	Per 10-fold increase	0.246 (0.168)	1.279 [0.912, 1.795]	0.150
Adjusting for plasma HIV RNA for HIV+ participants				
CSF MCP-1	Per 1,000 pg/ml increase	0.314 (0.075)	1.369 [1.177, 1.592]	**< 0.001**
Plasma MCP-1	Per 1,000 pg/ml increase	-0.797 (0.667)	0.451 [0.118, 1.726]	0.238
CSF Neopterin	Per 10 nmol/l increase	0.434 (0.063)	1.543 [1.360, 1.750]	**< 0.001**
Plasma Neopterin	Per 10 nmol/l increase	0.121 (0.075)	1.128 [0.971, 1.311]	0.113
CSF TNFα	Per 10 pg/ml increase	0.833 (0.225)	2.300 [1.462, 3.616]	**< 0.001**
Plasma TNFα	Per 10 pg/ml increase	0.083 (0.071)	1.087 [0.943, 1.253]	0.244
CSF sCD14	Per 10,000 pg/ml increase	0.106 (0.021)	1.112 [1.065, 1.161]	**< 0.001**
Plasma sCD14	Per 100,000 pg/ml increase	0.036 (0.026)	1.037 [0.984, 1.093]	0.173
Adjusting for CSF HIV RNA for HIV+ participants				
CSF MCP-1	Per 1,000 pg/ml increase	0.249 (0.070)	1.283 [1.115, 1.476]	**< 0.001**
Plasma MCP-1	Per 1,000 pg/ml increase	-0.738 (0.586)	0.478 [0.147, 1.556]	0.215
CSF Neopterin	Per 10 nmol/l increase	0.426 (0.084)	1.532 [1.293, 1.814]	**< 0.001**
Plasma Neopterin	Per 10 nmol/l increase	0.074 (0.067)	1.077 [0.940, 1.233]	0.279
CSF TNFα	Per 10 pg/ml increase	0.468 (0.282)	1.597 [0.905, 2.818]	0.104
Plasma TNFα	Per 10 pg/ml increase	0.023 (0.064)	1.024 [0.900, 1.164]	0.718
CSF sCD14	Per 10,000 pg/ml increase	0.087 (0.024)	1.091 [1.040, 1.144]	**< 0.001**
Plasma sCD14	Per 100,000 pg/ml increase	0.023 (0.024)	1.023 [0.976, 1.073]	0.335
HIVnegative participants				
CSF MCP-1	Per 1,000 pg/ml increase	0.623 (0.177)	1.864 [1.307, 2.659]	**< 0.001**
Plasma MCP-1	Per 1,000 pg/ml increase	0.938 (0.825)	2.555 [0.486, 13.429]	0.261
CSF Neopterin	Per 10 nmol/l increase	1.709 (0.621)	5.525 [1.584, 19.269]	**0.008**
Plasma Neopterin	Per 10 nmol/l increase	0.192 (0.304)	1.211 [0.657, 2.232]	0.532
CSF TNFα	Per 10 pg/ml increase	2.337 (0.736)	10.345 [2.356, 45.430]	**0.003**
Plasma TNFα	Per 10 pg/ml increase	0.042 (0.061)	1.043 [0.923, 1.178]	0.489

Notes: Significant P values (<0.05) are in bold font.
Abbreviations: SE = Standard error; CI = confidence interval; pg = picograms; ml = milliliter; nmol = nanomole. All models are adjusted for age, race, and gender.

Supplemental Table C. (Top panel) Results of linear regression analyses for association of change in natural log transformed CSF NFL between two visits (loge CSF NFL at second visit – loge CSF NFL at baseline) with CSF/plasma biomarker value *at baseline* in HIV+ participants. (Bottom panel) Results of BMA method for assessing association of change in natural log transformed CSF NFL between two visits with a set of baseline covariates. E(β\|Data) denotes the posterior weighted average of the model-specific point estimates of the coefficient across all possible multiple linear regression models that can be formed using 13 covariates[a] in HIV+ participants. SD[β\|Data] denotes the posterior standard deviation of β. Only the covariates with posterior effect probability (PEP), P($\beta \neq 0$ \|D), greater than 0.5 are reported.

One biomarker per each model[b]				
Biomarker	**Unit**	**β (SE)**	**e^{β} [95% CI]**	**P**
CSF MCP-1	Per 1,000 pg/ml increase	-0.217 (0.059)	0.805 [0.712, 0.91]	**0.001**
Plasma MCP-1	Per 1,000 pg/ml increase	0.218 (0.586)	1.244 [0.372, 4.158]	0.713
CSF Neopterin	Per 10 nmol/l increase	-0.277 (0.056)	0.758 [0.676, 0.850]	**< 0.001**
Plasma Neopterin	Per 10 nmol/l increase	-0.130 (0.123)	0.878 [0.681, 1.131]	0.299
CSF TNFα	Per 10 pg/ml increase	-0.265 (0.208)	0.767 [0.500, 1.178]	0.215
Plasma TNFα	Per 10 pg/ml increase	0.003 (0.007)	1.003 [0.989, 1.018]	0.639
CSF sCD14	Per 100,000 pg/ml increase	-0.541 (0.204)	0.582 [0.382, 0.887]	**0.014**
Plasma sCD14	Per 100,000 pg/ml increase	-0.015 (0.025)	0.985 [0.937, 1.036]	0.551
CSF HIV RNA	Per 10-fold increase	-0.389 (0.143)	0.678 [0.505, 0.910]	**0.012**
Plasma HIV RNA	Per 10-fold increase	-0.305 (0.172)	0.737 [0.517, 1.050]	0.088

All baseline biomarker data and clinical variables considered by BMA method				
Covariate	Unit	**E[β|Data] (SD[β|Data])**	**exp(E[β|Data])**	**P($\beta \neq 0$ |D)**
CSF MCP-1	Per 1,000 pg/ml increase	-0.198 (0.113)	0.820	**0.854**
CSF Neopterin	Per 10 nmol/l increase	-0.129 (0.109)	0.879	0.697

Significant P values (<0.05) and PEPs higher than 0.75 are in bold font.
Abbreviations: CI = confidence interval; BMA = Bayesian Model Averaging; PEP = Posterior Effect Probability
[a]Age, race, gender, CSF MCP-1, Plasma MCP-1, CSF Neopterin, Plasma Neopterin, CSF TNFa, Plasma TNFa, CSF sCD14, Plasma sCD14, CSF HIV RNA and Plasma HIV RNA (all CSF and Plasma biomarkers are baseline values).
[b]All models are adjusted for age, race, and gender.

Supplemental Table D. (Top panel) Results of linear regression analyses for association of change in NPT9 between two visits (NPT9 at second visit – NPT9 at baseline) with *change in each CSF/plasma biomarker between the two visits* in HIV+ participants

One biomarker per each model[a]				
Biomarker	**Unit**	**β (SE)**	**95% CI**	**P**
CSF MCP-1	Per 1,000 pg/ml greater decrease between two visits	0.32 (0.54)	[-0.79, 1.43]	0.559
Plasma MCP-1	Per 1,000 pg/ml greater decrease between two visits	2.00 (4.73)	[-7.74, 11.73]	0.677
CSF Neopterin	Per 10 nmol/l greater decrease between two visits	-0.39 (0.50)	[-1.42, 0.64]	0.442
Plasma Neopterin	Per 10 nmol/l greater decrease between two visits	-0.83 (1.01)	[-2.91, 1.25]	0.420
CSF TNFα	Per 10 pg/ml greater decrease between two visits	-1.38 (1.30)	[-4.05, 1.29]	0.298
Plasma TNFα	Per 10 pg/ml greater decrease between two visits	-0.96 (0.76)	[-2.52, 0.59]	0.214
CSF sCD14	Per 100,000 pg/ml greater decrease between two visits	-0.51 (0.34)	[-1.20, 0.18]	0.138
Plasma sCD14	Per 100,000 pg/ml greater decrease between two visits	-0.11 (0.17)	[-0.46, 0.24]	0.524
CSF HIV RNA	Per 10-fold greater decrease between two visits	-2.28 (0.88)	[-4.09, -0.48]	**0.015**
Plasma HIV RNA	Per 10-fold greater decrease between two visits	-0.89 (1.07)	[-3.09, 1.30]	0.411

Significant P values (<0.05) and PEPs higher than 0.75 are in bold font.
Abbreviations: SE = standard error; CI = confidence interval
[a]All models are adjusted for age, race, and gender.

Supplemental Table E. Results of linear regression analyses for association of change in NPT9 between two visits (NPT9 at second visit – NPT9 at baseline) with CSF/plasma biomarker value *at baseline* in HIV+ participants.

One biomarker per each model				
Biomarker	**Unit**	**β (SE)**	**95% CI**	**P**
CSF MCP-1	Per 1,000 pg/ml increase	0.42 (0.43)	[-0.47, 1.31]	0.340
Plasma MCP-1	Per 1,000 pg/ml increase	3.66 (3.45)	[-3.43, 10.75]	0.298
CSF Neopterin	Per 10 nmol/l increase	-0.12 (0.48)	[-1.11, 0.87]	0.804
Plasma Neopterin	Per 10 nmol/l increase	-0.45 (0.75)	[-2.00, 1.10]	0.557
CSF TNFα	Per 10 pg/ml increase	-0.71 (1.30)	[-3.39, 1.97]	0.589
Plasma TNFα	Per 10 pg/ml increase	-0.03 (0.04)	[-0.12, 0.06]	0.469
CSF sCD14	Per 100,000 pg/ml increase	0.16 (1.43)	[-2.79, 3.11]	0.912
Plasma sCD14	Per 100,000 pg/ml increase	0.05 (0.15)	[-0.25, 0.35]	0.716
CSF HIV RNA	Per 10-fold increase	-1.50 (0.93)	[-3.42, 0.42]	0.121
Plasma HIV RNA	Per 10-fold increase	-0.38 (1.12)	[-2.67, 1.91]	0.735

Significant P values (<0.05) are in bold font.
Abbreviations: SE = standard error; CI = confidence interval
[a]Age, race, gender, CSF MCP-1, Plasma MCP-1, CSF Neopterin, Plasma Neopterin, CSF TNFa, Plasma TNFa, CSF sCD14, Plasma sCD14, CSF HIV RNA and Plasma HIV RNA (all CSF and Plasma biomarkers are baseline values).