Genetic Influence on CSF and Plasma Biomarker Stability Over 12 Years in People With HIV

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BACKGROUND

- People with HIV (PWH) on effective antiretroviral therapy (ART) experience persistent inflammation and neuro-degeneration, contributing to "inflammaging" and comorbid disorders.
- Key biomarkers of inflammation (e.g., sTNFR-II) and neurodegeneration (e.g., neurofilament light [NFL]) remain elevated compared to HIV-uninfected individuals, even when plasma HIV RNA is undetectable.
- Our recent analysis of the CHARTER cohort demonstrated remarkable 12-year stability in these biomarkers despite significant improvements in viral control.
- **Hypothesis:** Intrinsic factors, particularly host genetics, establish biological "set points" that are resistant to therapeutic intervention.

METHODS

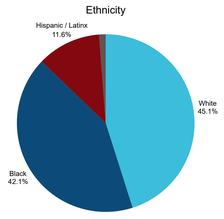
Study Design & Cohort Selection

Prospective, observational CHARTER cohort (N=308)
↓ Missing paired longitudinal biomarker samples or genotype data.
Complete baseline and 12-year follow-up data (N=164)

Baseline Demographics

- Age: Median 44.1 years.

♂80.5% ♀19.5%



Biomarker & Genetic Profiling

- 24 aging-relevant markers (12 plasma, 12 CSF).
- Quantified via matrix-validated Luminex, MSD, and ELISA platforms.
- Analyzed 19 SNPs associated with neurodegeneration, amyloid processing, and inflammation pathways.

Statistical Modeling

- Linear mixed-effects models with a random intercept for each participant to account for repeated measures.
- Covariates: Adjusted for age, sex, estimated duration of infection, ART duration, and plasma viral load. Continuous data were log10-transformed, Box-Cox adjusted, and standardized.
- Significance: Controlled using False Discovery Rate (FDR) correction.

Host genetic variants are associated with long-term 'set point' stability of neuroinflammation and axonal injury biomarkers in PWH on suppressive ART.

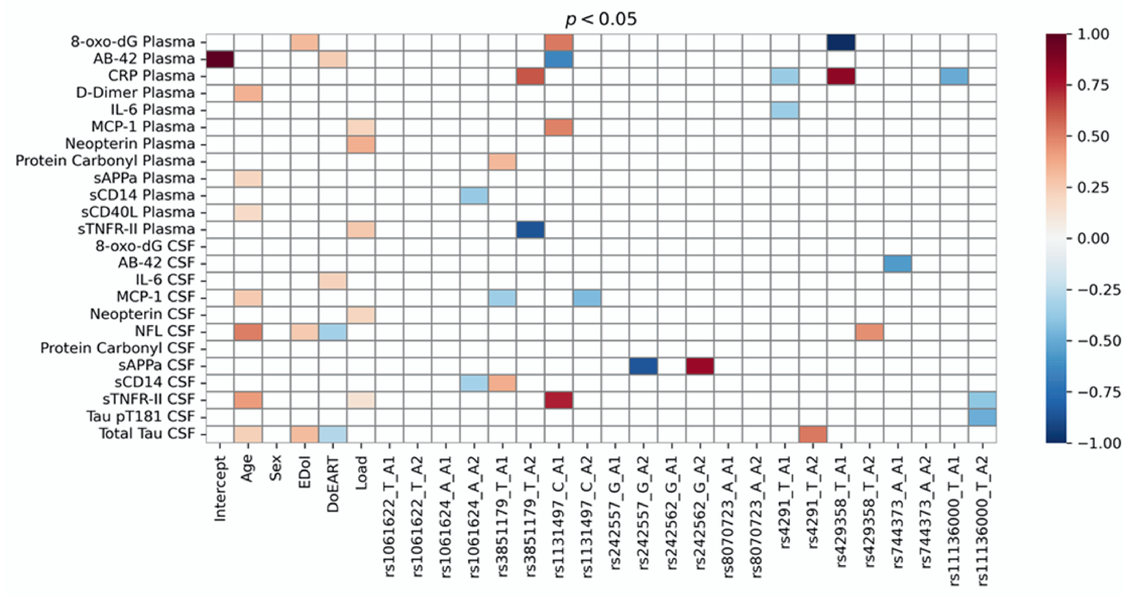


Figure 1. Heatmap of standardized fixed-effect coefficients showing significant associations ($p < 0.05$) between clinical/genetic predictors and biomarker concentrations. Red indicates positive effects, and blue indicates negative effects.

Gene / SNP (allele)	Biomarker	β (95% CI)	Direction	p-value	Known Role	Interpretation in this Study
MAPT *rs8070723 (T)*	CSF neurofilament light	−0.42 (−0.72 to −0.12)	lower residuals	0.007	Tags H1/H2 haplotype inversion; H1 associated with higher tau expression and tauopathy risk	Carriers of the H2 haplotype (T allele) had persistently lower NFL, suggesting a protective effect on axonal integrity in PWH
TNFRSF1B *rs1061622 (G)*	Plasma sTNFR-II	+0.28 (0.15 to 0.41)	higher residuals	1.2×10^{-5}	Missense variant (M196R) altering TNFR2 shedding; modulates TNF-α signaling	G allele carriers showed higher sTNFR-II, consistent with genetically determined inflammatory "set points"
PICALM *rs3851179 (A)*	Plasma sTNFR-II	−0.21 (−0.35 to −0.07)	lower residuals	0.004	Endocytic adaptor; enhances Aβ clearance and supports microglial function	Protective A allele linked to lower systemic inflammation (reduced sTNFR-II) beyond its amyloid role
PICALM *rs3851179 (A)*	CSF neopterin	−0.19 (−0.33 to −0.05)	lower residuals	0.009		Protective A allele also associated with reduced microglial activation, suggesting cross-pathway anti-inflammatory effects
SORL1 *rs1131497 (C)*	Plasma $A\beta_{42}$	+0.25 (0.11 to 0.39)	higher residuals	0.0005	APP trafficking receptor; dysfunction increases amyloidogenic processing	C allele carriers had higher $A\beta_{42}$, consistent with enhanced amyloid release
SORL1 *rs1131497 (C)*	CSF MCP-1	+0.22 (0.08 to 0.36)	higher residuals	0.002		The same allele also predicted higher MCP-1, linking amyloid dysregulation to downstream inflammation

Table 1: Significant Genetic Determinants of 12-Year Biomarker Stability. Results from linear mixed-effects models after False Discovery Rate (FDR) correction.

RESULTS

Key Findings

- Biomarker Stability: Aging-related biomarkers remained highly stable over 12 years (ICC > 0.6), despite viral suppression improving from 62% to 73.4%.
- Genetic Determinants: Six significant SNP-biomarker associations were identified using linear mixed-effects modeling (FDR-corrected).

Mechanistic Highlights

- Neuroprotection (MAPT rs8070723): Heterozygotes (H2 haplotype) showed markedly lower CSF NFL, indicating long-term axonal protection.
- H2-enriched subgroup showed ~35% lower CSF NFL
- Anti-Inflammation (PICALM rs3851179): The protective A allele linked amyloid clearance mechanisms to reduced systemic and microglial inflammation.
- Amyloid-Inflammation Axis (SORL1 rs1131497): The risk allele predicted both enhanced amyloid processing (higher Aβ42) and secondary inflammatory activation (higher MCP-1).

CONCLUSIONS

- Host genetics are associated with the long-term stability of neuroinflammatory and neurodegenerative biomarkers in PWH, potentially establishing individualized set points despite ART.
- These exploratory findings uncover novel cross-pathway interactions, such as the link between the *PICALM* gene and inflammatory markers, while confirming established biological pathways.
- Given the exploratory nature of this study, replication in larger, more diverse cohorts of PWH and functional validation studies are necessary to confirm these genetic pathways in the unique context of HIV

ADDITIONAL KEY INFORMATION

- **Contact:** *dlimajunior@health.ucsd.edu*

PLAIN LANGUAGE SUMMARY

Even after 12 years of effective HIV treatment, patients show consistent, individualized levels of inflammation and brain injury markers. We discovered that specific genetic variations help determine these permanent biological "set points," suggesting a person's genetics play a crucial role in their long-term neurological health.