Assessing blood-based biomarkers as predictors of cognitive decline in PWH in ACTG A5322 (HAILO) 546

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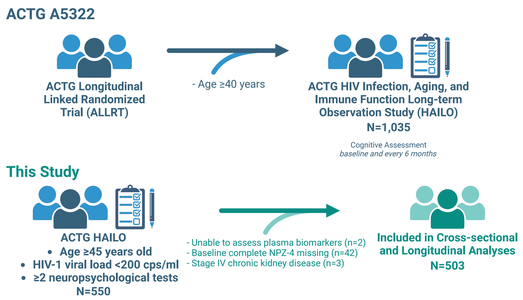
BACKGROUND

Blood-based biomarkers such as neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) are under investigation for use in memory clinics. While NfL is associated with dementia in people with HIV (PWH), its utility as a clinical biomarker for cognitive decline remains insufficiently studied. Similarly, data on the cognitive performance and GFAP levels in PWH on ART are limited.

We investigated the relationship between plasma NfL and GFAP values and change in neuropsychological (NP) performance among virologically suppressed PWH aged 45 years or older in the AIDS Clinical Trials Group (ACTG) HIV Infection, Aging, and Immune Function Long-term Observation Study (HAILO) A5322.

COHORT DESCRIPTION & METHODS



- HAILO investigators provided NP z-scores (NPZ-4), cognitive status and clinical data.
- NPZ-4 scores are based on four NP tests standardized as z-scores. Individuals with two NP scores below -1 SD or one score below -2 SD were classified in HAILO as impaired. Lower NPZ-4 score indicates worse performance.
- Biomarkers were quantified using the Simoa assay.
- Log_{10} transformed NfL and GFAP values were used for regression analyses.

Linear regression models were fitted to test the associations between NP performance and NfL or GFAP.

- Cross-sectional analyses: NPZ-4 score at plasma was defined as baseline, and models adjusted for age, sex at birth, race, and years of education (Model I); additional adjustment included CD4+ T-cell nadir, ART duration, and estimated glomerular function (Model II).
- Longitudinal analyses: NPZ-4 scores were summarized by calculating the slope for each participant (NPZ-4 slope). Models I and II were additionally adjusted for baseline NPZ-4 and weighted by number of visits.

MAIN FINDINGS

- Cross-sectionally, higher NfL and GFAP were associated with worse cognitive performance.
- Longitudinally, higher baseline NfL was statistically associated with subsequent cognitive decline, but the magnitude of the association was small.
- There was no association between baseline GFAP and future cognitive performance.

RESULTS-CLINICAL DATA & CROSS-SECTIONAL ANALYSIS

Table 1. Clinical Characteristics

Sample characteristic	Overall (n=503)	Cognitive Function: Impaired (n=132)	Cognitive Function: Not impaired (n=371)
Sociodemographics			
Age, years	52 [48, 57]	52 [49, 57]	52 [48, 57]
Race/ethnicity			
White non-Hispanic	268 (53.3)	**59 (44.7)**	**209 (56.3)**
Black non-Hispanic	131 (26.0)	**20 (15.2)**	**111 (29.9)**
Hispanic	104 (20.7)	**53 (40.2)**	**51 (13.7)**
Medical history			
Chronic kidney disease			
Stage 1 (eGFR >90)	255 (50.7)	77 (58.3)	178 (48.0)
Stage 2 (eGFR 60-89)	210 (41.7)	48 (36.4)	162 (43.7)
Stage 3 (eGFR <60)	38 (7.6)	7 (5.3)	31 (8.3)
HIV characteristics			
CD4 count, cells/mm^3	661.00 [499.50, 864.75]	701.50 [528.25, 929.50]	644.00 [485.25, 846.00]
CD4 nadir, cells/mm^3			
≥200	254 (50.5)	**77 (58.3)**	**177 (47.7)**
<200	246 (48.9)	**53 (40.2)**	**193 (52.0)**
Unknown	3 (0.6)	**2 (1.5)**	**1 (0.3)**
ART duration, years	8.60 [5.50, 12.15]	8.10 [4.97, 12.22]	8.70 [5.70, 12.10]
NP testing			
NP test visits, count	7.00 [6.00, 8.00]	6.00 [5.00, 8.00]	7.00 [6.00, 8.00]
Observation duration, years	5.91 [5.41, 7.34]	**5.72 [5.00, 7.16]**	**5.97 [5.43, 7.37]**
Years of education	14.00 [12.00, 16.00]	14.00 [12.00, 16.00]	14.00 [12.00, 16.00]
NPZ-4	0.10 [-0.48, 0.75]	**-0.88 [-1.40, -0.57]**	**0.42 [-0.04, 0.98]**
NfL, pg/mL	1.03 [0.90, 1.16]	**1.07 [0.95, 1.20]**	**1.02 [0.89, 1.15]**
GFAP, pg/mL	1.89 [1.77, 2.03]	1.92 [1.78, 2.09]	1.89 [1.77, 2.02]

Variable distributions are reported as n (%) for categorical variables and median [IQR] for continuous variables. Boldface denotes a statistically significant (p<0.05) difference between the cognitively "impaired" and "not impaired" groups.

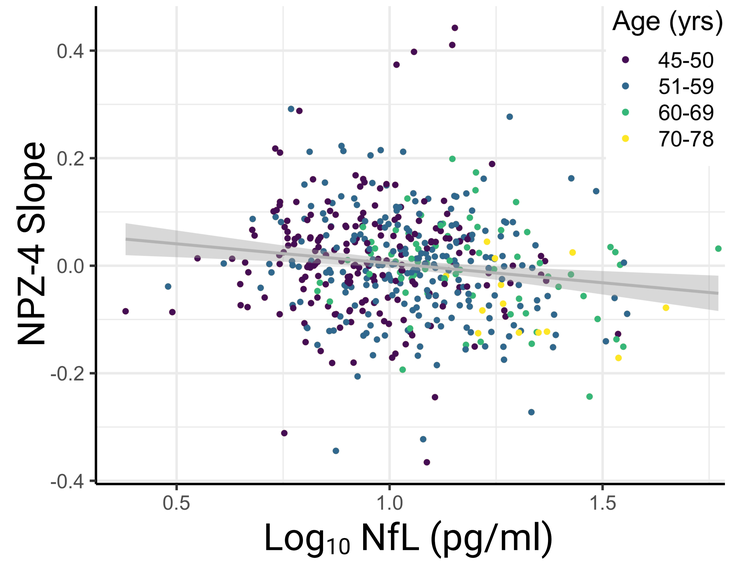
Table 2. Cross-Sectional Associations: NPZ-4 Score with Baseline Biomarkers

	Unadjusted β (95% CI)	Adjusted: Model I β (95% CI)	Adjusted: Model II β (95% CI)
NfL	**-0.670 (-1.079, -0.261)**	**-0.693 (-1.152, -0.233)**	**-0.839 (-1.310, -0.368)**
GFAP	**-0.596 (-0.957, -0.236)**	**-0.434 (-0.820, -0.049)**	**-0.542 (-0.935, -0.148)**

Covariates for models are defined in Methods: Cross-Sectional Analyses; Boldface denotes p<0.05

RESULTS-LONGITUDINAL ANALYSIS

Figure 1. Relationship between NPZ-4 slope and Baseline NfL



The scatterplot shows the regression line with 95% confidence band around the predicted value between NPZ-4 slope and baseline NfL. Each dot represents a participant, and color denotes age categories.

Table 3. Longitudinal Associations: NPZ-4 Slope with Baseline Biomarkers

	Unadjusted β (95% CI)	Adjusted: Model I β (95% CI)	Adjusted: Model II β (95% CI)
NfL	**-0.077 (-0.119, -0.036)**	**-0.080 (-0.126, -0.034)**	**-0.078 (-0.126, -0.030)**
GFAP	-0.040 (-0.076, -0.004)	-0.036 (-0.075, 0.002)	-0.032 (-0.072, 0.007)

Covariates for models are defined in Methods: Longitudinal Analyses; Boldface denotes p<0.05

CONCLUSION

In a cohort of PWH on ART and median age of 52 yrs:

The **cross-sectional** relationship showed lower (worse) cognitive scores was associated with higher NfL and GFAP, after adjustment for demographic, HIV-associated factors and kidney function.

The **longitudinal** relationship over a mean follow-up time of 5.9 yrs showed a negative NPZ-4 slope (decline in NP performance) correlated with higher baseline NfL (0.08 unit decrease/year for 1 unit increase in NfL).

The NPZ-4 slope did not correlate with GFAP.

IMPLICATIONS

The weak associations between NP performance and plasma NfL or GFAP suggest that relying solely on either as clinical biomarkers may not offer healthcare providers substantial additional insights into future cognitive decline among PWH on ART during the age ranges examined.

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