Plasma CNS Tissue Markers in Heavily Treatment-Experienced PWH in the PRESTIGIO Registry

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BACKGROUND

- Heavily treatment-experienced (HTE) persons with HIV (PWH) are characterized by long infection and treatment history, resistant viruses, and a significant burden of concomitant diseases.
- Since these features may be associated with HIV replication in the Central Nervous System (CNS), this study aimed to assess plasma CNS tissue markers in HTE versus controls.

METHODS

- HTE cases were selected from the PRESTIGIO registry (Italian multicenter cohort enrolling PWH with documented four-class drug resistance) and stratified according to HIV RNA below (VS) or above 50 c/mL (VF) in their first sample in 2021-2023.
- Controls were consecutively treated >50-year-old PWH with VS from San Raffaele Hospital in Milan.
- PWH with ongoing CNS disorders were excluded.
- Plasma samples were analyzed by SIngle MOlecule Array (SIMOA SR-X, Quanterix Corp., Boston, MA, USA) for biomarkers associated with: neuronal damage (neurofilament-light chain, “NFL” and total Tau protein, “tau”), astrocyte activation (Glial Fibrillary Acidic Protein, “GFAP”), ubiquitin-proteasome involvement (Ubiquitin C-terminal Hydrolase, “UCH-L1”).

RESULTS

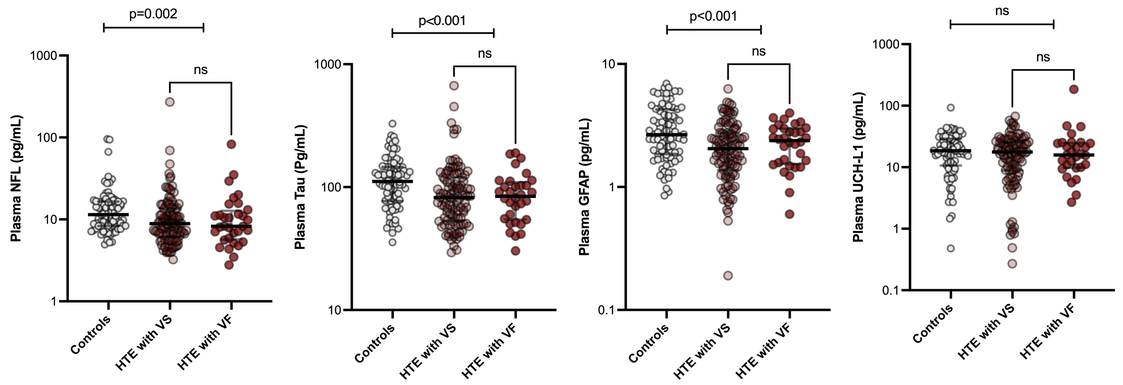
- We included 84 controls, 106 HTE/VS, and 32 HTE/VF whose features are shown in the Table
- HTE/VF showed HIV RNA <200 (14, 43.8%), 200-999 (5, 15.6%) or >1000 copies/mL (13, 40.6%).

	Controls n= 84	HTE with VS n= 106	HTE with VF n= 32	P values *
Age: years	59.5 (55.6-62.2)	58.5 (53.5-62.1)	54.7 (48.8-61.6)	0.140
Male sex (nr, %)	55 (65.5%)	71 (67%)	29 (90.6%)	0.021
BMI: Kg/m^2	25.6 (23.3-27.8)	24.2 (21.9-26.8)	23.5 (21.6-25.3)	0.069
Self-reported way of HIV acquisition (nr, %)				
Heterosexual	21 (25%)	28 (26.4%)	6 (18.8%)	0.678
Homosexual	29 (34.5%)	25 (23.6%)	8 (25%)	0.229
IVDU	8 (9.5%)	7 (6.6%)	3 (9.4%)	0.903
At birth	0 (0%)	8 (7.5%)	5 (15.6%)	0.003
Years of HIV infection	26.3 (19.2-32.8)	30.2 (25.4-33.6)	29.2 (23.5-33.5)	0.011
Nadir CD4 cell count: n/mm3	248 (151-365)	119 (27-216)	45 (9-116)	<0.001
Current CD4 cell count: n/mm3	792 (618-942)	685 (482-889)	276 (106-436)	<0.001

Values: medians (25-75th IQR) or number (%); * Kruskal-Wallis or Chi-square

Heavily treatment-experienced persons with documented HIV four-class drug resistance do not show higher plasma biomarkers of neuronal damage (NFL and tau), astrocyte activation, or ubiquitin-proteasome dysfunction

RESULTS (continued)



- Biomarker levels in the three groups are shown in the figure above (p values refers to Mann-Whitney tests for pairwise comparisons of controls vs. HTE and HTE/VS vs. HTE/VF)
  - NFL, tau and GFAP levels were significantly lower in HTE than in controls
  - Significant correlations between the four markers were observed (Spearman’s test, all p <0.001)
- Significant bivariate correlations were observed:
  - Higher age correlated to higher NFL (p<.001), GFAP (p<.001) and UCH-L1 (p=.040)
  - Male sex with lower GFAP (p=.018) and tau (p<.001)
  - HIV acquired at birth with lower GFAP (p=.012).
  - In HTE/VF plasma HIV RNA inversely correlated to NFL (p=.048).

RESULTS (continued)

Antiretroviral drugs other than NRTIs: current use of (nr, %)				
	Controls n= 84	HTE with VS n= 106	HTE with VF n= 32	P values *
Dolutegravir	26 (31%)	86 (81.1%)	23 (71.9%)	<0.001
Bictegravir	21 (25%)	8 (7.5%)	2 (6.3%)	0.001
Darunavir	5 (6%)	78 (73.6%)	22 (68.8%)	<0.001
Doravirine	10 (11.9%)	8 (7.5%)	7 (21.9%)	0.078
Fostemsavir	0 (0%)	8 (7.5%)	3 (9.4%)	0.027
Lenacapavir	0 (0%)	1 (0.9%)	1 (3.1%)	0.281

Values: medians (25-75th IQR) or number (%); * Kruskal-Wallis or Chi-square

- In HTE, lower tau was associated with fostemsavir (p=.049) and doravirine use (p=.037) and lower GFAP with darunavir (p=.009).
- Multivariate linear regression, corrected for age, sex, study group, body mass index (BMI) and significant variables at bivariate analyses, was performed to identify predictors of high levels of each marker

NFL	Tau	GFAP	UCH-L1
BMI p=0.040, B 0.929, 95%CI 0.045-1.814	**CD4 nadir** p=0.002; B 0.002, 95%CI 0.001-0.003	**Age** p<0.001; B 4.74, 95%CI 3.63-6.01)	**GFAP** p=0.014, B 0.070, 95%CI 0.014-0.122)
GFAP p<0.001; B 0.119, 95%CI 0.057-0.181	**Current CD4** p=0.009; B -0.001, -0.229, 95%CI -0.002-0.000	**BMI** p=0.009; B -2.45, 95%CI -4.90-0.70	
	Male sex p=0.003; B -0.727, 95%CI -1.199-0.255)	**Male sex** p=0.011; B -26.43, 95%CI -40.85-5.33)	
		HIV acquisition at birth p<0.001; B 79.19, 95%CI 36.64-135.90)	

CONCLUSIONS

- Plasma CNS tissue marker levels do not support higher CNS injury risk in HTE-PWH.
- Several other variables seem independently and variably associated with higher levels of each marker.
  - Some gender differences were observed with males showing lower levels of tau and GFAP
  - Participants who had acquired HIV at birth (despite being only 13) showed lower GFAP levels and similar concentrations of the other biomarkers
- The observed differences according to antiretroviral use deserve further prospective evaluation

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