

Mild HIV-Associated Neurocognitive Disorder persists despite very low levels of HIV RNA activity in plasma and cerebrospinal fluid

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for the **CNS HIV Latency Identification (CHIEF) Group**

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Introduction

HIV-associated neurocognitive disorder (HAND) persists in a clinically mild form despite HIV suppression at standard detection limits (<20cp/mL) in both blood and cerebrospinal fluid (CSF).

It is unclear whether HAND persists at very low levels of viral suppression (<1cp/mL)

It is also unclear if very low residual CSF compartmentalization increases HAND risk compared to residual viral load that is non-compartmentalized or restricted to plasma only

Methods

- Exploratory analysis of 14 virally-suppressed (<20cp/mL in blood and CSF) HIV+ men
- Levels of HIV RNA in plasma and CSF samples analysed using a single copy assay (SCA) with detection limits of 0.2cp/mL for plasma and 0.3cp/mL for CSF
- Plasma and CSF HIV RNA SCA dichotomized according to <1 and ≥1 cp/mL cut-off to create 4 plasma/CSF compartmentalization groups
- All completed standard neuropsychological (NP) testing measuring 7 cognitive domains. Mild HAND was defined per FRASCATI criteria using Global Deficit Score (GDS) methodology:
 - GDS≥0.5 and no IADL decline = ANI
 - GDS≥0.5 and decline in at least 2 IADLs = MND
 - GDS≥1.5 and decline in at least 2 IADLs = HAD

Results

•Using standard criteria, mild HAND was present in 43% of the sample (ANI=36%, MND=7%) and 3/4 compartmentalization groups (see Table 1)

•Plasma+/CSF+ showed elevated CSF protein and CSF/serum albumin ratio compared to the other groups (see Figure 1)

•HIV infection duration was an average 10 years longer and nadir CD4 was lower in Plasma+/CSF+ group

•Lower CD4:CD8 ratio was associated with CSF HIV RNA above 1cp/mL (see Figure 2)

Table 1. HAND status according to HIV RNA SCA compartmentalization

	Plasma-/CSF- (n=7)	Plasma+/CSF- (n=2)	Plasma-/CSF+ (n=3)	Plasma+/CSF+ (n=2)	p
HAND:NP-Normal	3:4	0:2	2:1	1:1	.52
ANI	2	0	2	1	.72
MND	1	0	0	0	
HAD	0	0	0	0	
Mean NP z-score	-0.5 (1.4)	0.92 (0.5)	0.03 (1.76)	-0.04 (1.18)	.30
GDS	0.38 (1.13)	0.03 (0.07)	0.5 (0.2)	0.43 (0.87)	.65

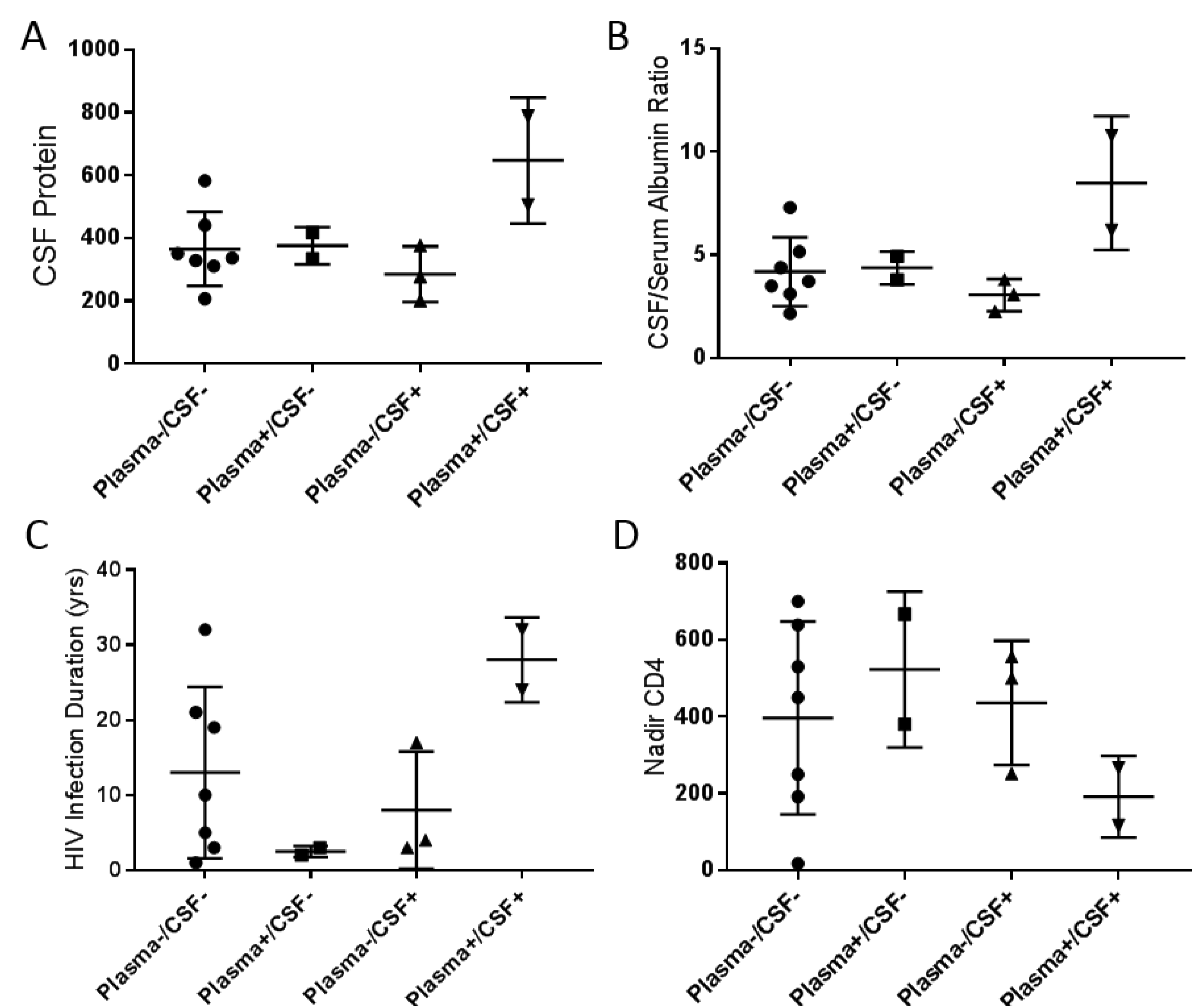


Figure 1. Elevated CSF protein and CSF/serum albumin ratio (B) in Plasma+/CSF+ compared to other groups (p<.05) suggests blood-brain barrier compromise. (C) Duration of HIV infection was much longer (p=.41) and (D) nadir CD4 was lower (p=.19) in the Plasma+/CSF+ group.

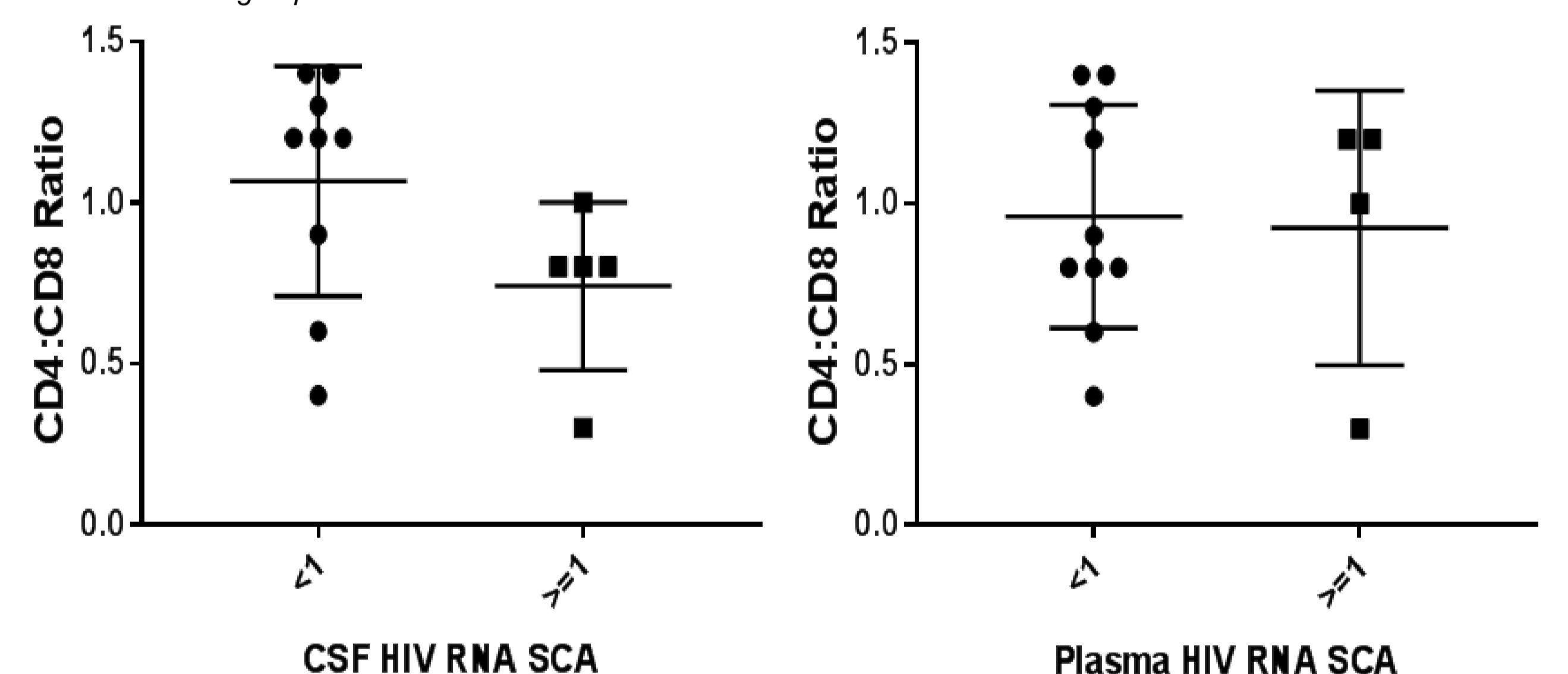


Figure 2. Low level residual HIV RNA in CSF (p=.02) but not plasma (p=.89) was associated with lower CD4:CD8 ratio (higher immune suppression)

Table 2. Sample Characteristics

	Plasma-/CSF- (n=7)	Plasma+/CSF- (n=2)	Plasma-/CSF+ (n=3)	Plasma+/CSF+ (n=2)	p
Age (years)	47 (13)	43.5 (3)	29 (44)	60.5 (11)	.50
Current CD4	795 (346)	704 (132)	876 (970)	551.5 (557)	.72
Current CD8	620 (431)	591 (96)	1062 (1157)	1021.5 (702)	.28
Plasma HIV RNA single copy Range	0.2 (0.7) (<0.2-0.89)	1.8 (1.2) (1.2-2.4)	0.2 (0.7) (<0.2-0.89)	2.8 (3.4) (1.1-4.5)	.02
CSF HIV RNA single copy Range	0.3 (0.41) (<0.3-0.7)	0.3 (0) (<0.3)	4.4 (4.3) (1.7-6)	2.9 (1.4) (2.2-3.6)	<.01

Note. All data presented as Med (IQR) unless otherwise specified. Compartmentalization groups did not differ with regards to demographic factors: education, sex, and ethnicity (ps=.51-.70).

Conclusion

- These data support that mild HAND can occur despite very low residual viremia in plasma or CSF and shows the need for larger studies.
- In a minority of cases, mild HAND seems to be driven by longer HIV duration and blood-brain barrier compromise. The underlying mechanisms remain to be fully elucidated for other cases.
- While indicative, it suggests that very low residual HIV RNA activity in the periphery is not the predominant contributor to mild HAND.

Acknowledgements

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