Poster 470

Panviral Antibody Reactome Profiles Associate With Cognition in People With HIV

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BACKGROUND

- Brain health disorders (BHDs) remain common in ART-suppressed PWH despite viral control
- Chronic viral coinfections shape immune function, yet their combined and domain-specific effects on cognition are poorly understood
- High-resolution, virome-wide epitope-level antibody profiling enables detection of distinct antiviral antibody signatures that may confer cognitive risk or protection.
- Hypothesis: BHDs reflect individualized antiviral immune response patterns rather than a single viral exposure

METHODS

Cohort

- Cross-sectional analysis
- 88 ART-suppressed PWH (CHARTER + HNRC)
- Paired CSF + plasma

Platform:

- VirSIGHT MIPSA (Infinity Bio) — antibody reactivity profiled against 286,793 DNA-barcoded viral peptides from >500 human viruses

Outcomes:

- Global + 7 cognitive domain impairment

Primary analyses: Welch's t-tests at two levels:

- *VARscore* — species-level aggregate antibody reactivity per virus
- *Peptide-level* — individual epitope reactivity across the full library

Sensitivity: Linear models adjusted for age, sex, CD4+

RESULTS

Cohort:

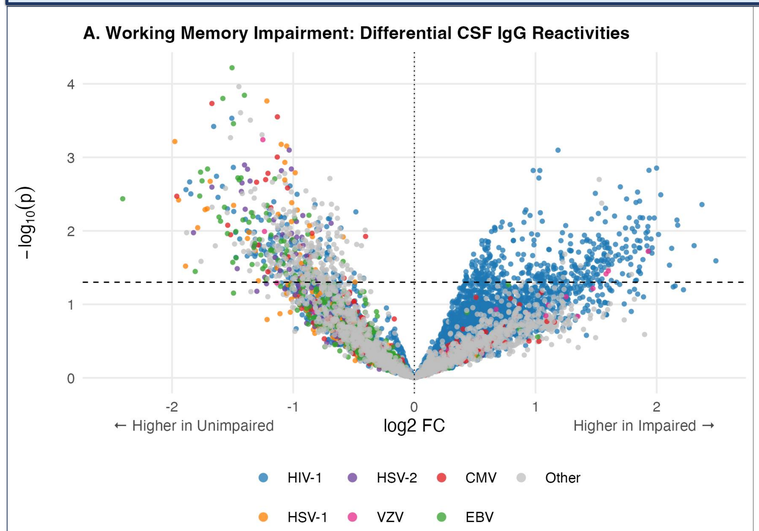
- Participants were predominantly male (81%) with mean age of 52, median CD4⁺ count of 680 (current) and 200/μL (nadir).

Global signal

- Total number of antibody reactivities (e.g.“total hits”) did **not** differ by impairment status.
- Suggests domain- and virus-specific effects rather than global immune senescence

In ART-suppressed PWH, antiviral antibody profiles associate with cognition in a virus-specific, bidirectional manner: broader herpesvirus responses track with intact cognition, while HIV-1 envelope responses track with impairment.

RESULTS: Peptide-Level Analysis



B. CSF peptide-level associations across cognitive domains

Cell text = # peptides (impaired | unimpaired) at p<0.05.

All unimpaired — Mixed — All impaired

	Global	Work Mem	Executive	SIP	Motor	Learning	Recall	Verbal
HIV-1	245 | 77	363 | 139	13 | 450	188 | 109	490 | 199	131 | 120	79 | 89	10 | 398
HSV-1	0 | 22	0 | 65	0 | 60	0 | 19	0 | 18	0 | 14	0 | 13	0 | 53
HSV-2	0 | 27	0 | 46	0 | 15	0 | 19	0 | 14	0 | 14	0 | 16	0 | 13
VZV	0 | 2	3 | 2	0 | 6		0 | 3			0 | 2
CMV	1 | 19	0 | 20	1 | 32	0 | 33	0 | 14	0 | 12	0 | 24	0 | 33
EBV	2 | 2	0 | 66	0 | 76	0 | 34	0 | 4	2 | 6	1 | 35	0 | 18
HBV		0 | 83	0 | 171	0 | 3				0 | 51

Peptide-Level Associations:

- Similar patterns observed across domains, strongest for working memory and executive function
- Working memory CSF showed strongest signal (figure A):
  - 942 peptides associated ($p<0.05$), none remained significant after FDR correction in this small study
- Enriched for HIV-1 and herpesvirus peptides
- HIV-1 had the most differentially reactive peptide responses and bidirectional
- Of the HIV antibodies associated with impairment, most were to envelope protein
- Most other viral reactivities associated with unimpaired performance
- Strong concordance between CSF and plasma
- Findings were similar in linear models adjusting for age, sex, CD4⁺

RESULTS: VARscore (Species-Level Analysis)

Only Working Memory and Executive Function showed significant associations after FDR correction:

Working Memory

CSF: HSV-1 (q=0.009), HSV-2 (q=0.009), EBV (q=0.039) → unimpaired

Plasma: HSV-1 (q=0.008), HSV-2 (q=0.025) → unimpaired

Executive Function

CSF: HSV-1 (q=0.034) → unimpaired

Plasma: HSV-1 (q=0.0056) → unimpaired

CONCLUSIONS

- High-resolution virome-wide antibody profiling identifies domain-specific, bidirectional antiviral immune signatures associated with cognition in ART-suppressed PWH - suggesting that the antiviral immune repertoire, not HIV alone, shapes cognitive heterogeneity in this population.
- **Working memory and executive function** showed the strongest, most reproducible associations
- **HSV-1** had the most consistent associations across domains and compartments, followed by HSV-2 and EBV —linked to *better* performance
- **HIV-1 envelope** antibody responses consistently tracked with *worse* cognition; non-envelope HIV and herpesvirus responses were enriched in unimpaired participants
- Total antibody reactivity burden did **not** differ by impairment status — arguing against global immune senescence and for virus-specific immune phenotypes

FUTURE DIRECTIONS

- Validate virus- and domain-specific antibody signatures in larger, longitudinal cohorts
- Characterize protective vs. risk antiviral immune phenotypes and their integration with markers of viral persistence, neuroinflammation, and host genetics.
- Leverage these findings to inform precision risk stratification and to explore whether modulating antiviral immunity can preserve brain health in PWH.

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