Machine Learning-Derived Cognitive Subtypes of HIV: Results From the NIMH MIAAD-NHIV Initiative

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BACKGROUND

- Cognitive symptoms affect 30-50% of people with HIV (PWH) despite effective use of antiretroviral therapy. These symptoms vary widely in their nature and severity, possibly reflecting differences in underlying mechanisms and risk factors.
- The heterogeneity observed in cognitive symptoms among PWH creates a challenge for translating research findings into effective clinical interventions.
- This study utilized a data-driven approach to identify cognitive subtypes and their clinical characteristics in an international sample of PWH who underwent cognitive assessment during acute or chronic infection.

METHODS

- Participants included 213 PWH including 180 virally suppressed individuals with chronic infection from two US cohorts (Washington University in St. Louis [WUSTL], n=100); CHARTER, n=80) and 33 with acute HIV (AHI) from the RV254 cohort in Thailand.
- Participants completed tests of verbal learning and memory, psychomotor speed (Digit Symbol, Trails A), verbal fluency, and fine motor speed (grooved pegboard). Individual test scores were scaled (M=10, SD=3) within each cohort prior to clustering.
- Cognitive data were reduced to 2-D using UMAP and clustered using Hierarchical Density Based Spatial Clustering of Applications with Noise (minimum number of points to form a cluster=5, minimum number of samples to define outliers=none, epsilon=0). The algorithm that yielded the largest minimal cluster size with a Silhouette score ≥0.60 was selected as the final cluster solution.

RESULTS

- Clustering revealed four cognitive subtypes (see Figure). Subtype 1 had the best performances with minimal variability across tests. Subtype 2 had lower learning, memory, and verbal fluency; subtype 3 had lower psychomotor and fine motor speed; subtype 4 had lower learning, memory, psychomotor on Digit Symbol and fine motor speed (ps<.05). Trails A scores were similar across subtypes.

Data-driven clustering identified four distinct cognitive subtypes in PWH. Subtypes differed on key sociodemographic factors and medical comorbidities.

Figure. Cognitive profiles by subtype.

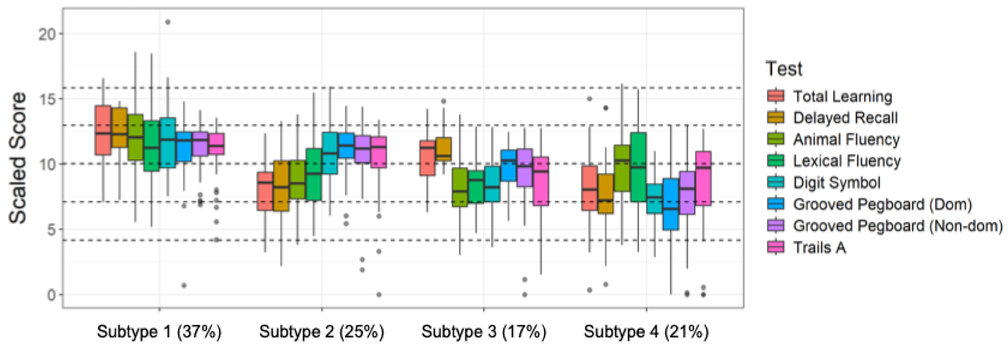


Fig. Subtype 1 had the highest test scores. Subtype 2 had a relative weakness on learning, memory, and verbal fluency; subtype 3 had a relative weakness on verbal fluency, psychomotor and fine motor speed; subtype 4 had the lowest scores except verbal fluency.

Table. Differences in demographic, biomarker and medical comorbidities across subtypes.

	Subtype 1	Subtype 2	Subtype 3	Subtype 4
CHARTER	33 (43.4%)	16 (29.1%)	13 (35.1%)	18 (40.0%)
RV254	12 (15.8%)	6 (10.9%)	11 (29.7%)	4 (8.9%)
WUSTL	31 (40.8%)	33 (60.0%)	13 (35.1%)	23 (51.1%)
Age	49.24 (14.87)	46.75 (13.93)	47.22 (17.57)	53.44 (10.85)
Minority race [a**,b***]	35 (46.1%)	41 (74.5%)	27 (73.0%)	38 (84.4%)
Education (12+ years) [b*]	71 (93.4%)	48 (87.3%)	31 (83.8%)	34 (75.6%)
CD4+ T-cell count (cells/μL)	621 (269)	661 (275)	528 (323)	635 (364)
Hematocrit % [a**,b*]	43.88 (4.08)	41.04 (4.76)	42.18 (4.96)	41.72 (4.55)
Hemoglobin [a**]	14.80 (1.57)	13.73 (1.78)	13.99 (1.63)	13.78 (1.64)
ALT [a**,b*]	30.68 (16.41)	21.87 (12.28)	31.22 (34.05)	26.30 (22.10)
AST/ALT Ratio [a**,b***]	1.02 (0.40)	1.19 (0.33)	1.22 (0.57)	1.44 (0.63)
HDL Cholesterol [a**]	48.14 (17.58)	54.91 (12.94)	49.69 (14.45)	53.47 (19.69)
Triglycerides [a*]	151.22 (104.52)	116.11 (95.47)	100.86 (39.52)	107.29 (44.51)
Hypertension [c*,c*]	29 (39.2%)	17 (31.5%)	14 (37.8%)	26 (61.9%)
Hepatitis C [c†]	15 (20.3%)	7 (13.0%)	11 (29.7%)	16 (38.1%)
Diabetes	12 (16.2%)	5 (9.3%)	5 (13.5%)	9 (21.4%)
Depression	11 (24.4%)	6 (27.3%)	9 (37.5%)	6 (27.3%)

[a]1vs2, [b]1vs4, [c]2vs4. ***p<.001, **p<.01, *p<.05, †p<.10. P-values were adjusted using FDR. Values are Mean (Standard Deviation) for continuous and N(%) for categorical variables.

CONCLUSIONS

- The presence of distinct cognitive subtypes among PWH contributes to heterogeneity in cognitive health when examined at the group level.
- Risk factors differed most between the cognitive subtypes with the highest vs. lowest test scores, and included demographic indices, health comorbidities (e.g., hypertension, HCV), and select lab values.
- Deeper phenotyping using machine learning and longitudinal analyses may help to identify “treatable traits” that can be targeted for future intervention studies.

PLAIN LANGUAGE SUMMARY

Multiple cognitive profiles exist among PWH. The profiles associate with different demographic and health-related risk factors that may help to inform the development of tailored interventions.

KEY CITATIONS

- Ellis et al.. AIDS. 2026, 1;40(3): 271-282.
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