The Veterans Aging Cohort Study Index Predicts Change in Neurocognitive Functions in People with HIV

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Background and Objectives

- The Veterans Aging Cohort Study (VACS) Index has been shown to predict mortality, morbidity, and functional performance in people with HIV.[1-3]
- Recent work from the CHARTER study has shown a cross-sectional association between higher VACS Index and increased risk of neuropsychological impairment.[4]
- This study examined the temporal association between the VACS index and neurocognitive functions and the potential clinical utility of the VACS index for assessing HIV-associated Neurocognitive Disorders (HAND).

Methods

Study sample

We recruited 543 adults from two HIV outpatient clinics in Toronto, Canada (Table 1). Participants were predominantly men (76%) on antiretroviral therapy (85%), and had an undetectable plasma HIV viral load (70%) at baseline.

Measures

Neuropsychological functions

Neuropsychological (NP) assessments were conducted annually using a brief battery that included:

- Hopkins Verbal Learning Test- Revised [5]
- Grooved Pegboard; [6] and
- WAIS-R Digit Symbol test[7-8]

Five Neuropsychological NP measures — HVLT-R total recall (correct responses), HVLT-R delayed recall (correct responses), Pegboard-dominant hand (seconds), Pegboard Non-dominant Hand (seconds), and Digit symbol (correct responses) — were obtained.

VACS Index

The VACS index was computed by summing pre-assigned risk points for age, CD4 count, plasma HIV viral load, haemoglobin, fibrosis, renal glomerular filtration, and HCV infection following guidelines.[1]

Medical comorbidities

We extracted data on medical comorbidities including cardiovascular diseases, hypertension, diabetes, and chronic lung diseases from clinical charts.

Demographic Variables

Demographic variables were collected from participants using standard instruments such as the Center for Epidemiologic Studies–Depression scale (CES-D)[9] and The Alcohol Use Disorder Identification Test (AUDIT).[10]

Statistical Analysis

Five raw NP measures were transformed into:

1) Z-scores (without demographic corrections), using the sample mean and standard deviation.
2) Age, gender, race, and education-corrected T-scores using published norms.[7,11-12]

Three different global NP function measures were created:

- Overall NP Z-score: Average of z-scores of the five NP measures
- Global T-score: Average of T-scores of the five NP measures (demographically corrected)
- Summary Regression-based Change Scores (sRCS): Average of residual regression scores of the five NP measures derived using standard regression-based (SRB) change score approach.[13]

Linear regression modelling was used to examine the association between VACS index score (at baseline) and change in NP functions over time, adjusting for baseline NP function and other covariates.

Table 1. Sample characteristics at baseline by VACS Index Quartile[a] (N=523)

Characteristics	Quartile 1 [0-6] n=141	Quartile 2 [7-15] n=112	Quartile 3 [16-27] n=140	Quartile 4 [28-100] n=130	p-value[b]
Age in years (mean, SD)	41	43	47	49	**<0.01**
Gender (male)	96%	80%	69%	66%	**<0.01**
Race/ethnicity (Caucasian)	61%	63%	56%	58%	0.61
Years of education (mean, SD)	13.9	13.6	13.2	13.6	0.15
Current cigarette smoker	28%	31%	34%	36%	0.49
Alcohol use, past year (AUDIT-10 ≥ 8)	18%	13%	17%	17%	0.63
Illicit drug use, past 6 months	22%	14%	14%	20%	0.19
Depressive symptoms (CESD-20 ≥16)	28%	29%	39%	34%	0.19
Recent CD4 count (≥ 500 cells/mm3)	58%	63%	34%	14%	**<0.01**
Nadir CD4 count (< 200 cells/mm3)	58%	48%	58%	70%	**<0.01**
Plasma HIV viral load (< 50 copies/ml)	91%	63%	71%	57%	**<0.01**
On antiretroviral therapy	98%	77%	81%	81%	**<0.01**
Years since HIV diagnosis (mean, SD)	10.0	9.6	11.3	10.6	0.22
Diagnosed with Hypertension (yes)	13%	21%	21%	26%	**0.05**
Cardiovascular disease (yes)[c]	6%	13%	11%	16%	0.09

a Mean and median for the total sample were 18.4 and 16, respectively. b Pearson Chi-Square test for categorical variables and ANOVA test for continuous variable c Angina, Angioplasty, Bypass surgery, Cardiovascular Accident, stroke, Congestive Heart Failure, Coronary Artery Disease, Myocardial Infarction, or Peripheral Vascular Disease

Note: Data for diabetes and Chronic Lung diseases is not presented due to small cell sizes.

Table 2. Distribution of VACS Index components at baseline (N=523)

Component	Level	n (%)	Component	Level	n (%)
Age (years)	<50	359 (69%)	Hemoglobin (g/dL)	> 14	319 (61%)
	50-64	144 (28%)		12-14	154 (29%)
	> 65	20 (4%)		10-12	43 (8%)
CD4 count (cells/mm3)	> 500	217 (42%)		< 10	7 (1%)
	350-499	151 (29%)	FIB-4	< 1.45	412 (79%)
	200-349	103 (20%)		1.45-3.25	98 (19%)
	100-199	32 (6%)		> 3.25	13 (3%)
	50-99	13 (3%)	eGFR (mL/min)	> 60	504 (96%)
	< 50	7 (1%)		45-60	14 (3%)
Plasma HIV viral load (copies/ml)	< 500	420 (80%)		<45	5 (1%)
	500-1x105	94 (18%)	Hepatitis C infection	61	61 (12%)
	> 1x105	9 (2%)			

Table 3. Results (unstandardized regression coefficient and p-value) from multivariate linear regression models with changes in NP functions as dependent variables (N=523)

Characteristics	Change in NP functions: Raw z-score (T2-T1) B	Raw z-score p-value	sRCS (T2-T1) B	sRCS p-value	Global T-score (T2-T1) B	Global T-score p-value
Baseline (T1) NP score [a]						
Z-score/T-score	-0.33	**<0.001**	**-0.27**	**<0.001**	**-0.09**	**0.004**
Demographic variables						
Gender (male)	0.03	0.789			**0.18**	**0.019**
Race (Caucasian)	**0.32**	**0.002**			**0.24**	**0.001**
Education (years)	0.02	0.311			0.01	0.282
Language spoken at home (English)	0.08	0.527	0.93	0.156	0.08	0.350
Cognitive/depressive symptoms						
Cognitive symptoms (MOS-COG score)	-0.03	0.501	-0.24	0.339	-0.02	0.615
Depression (CESD ≥16)	0.11	0.306	0.89	0.146	0.09	0.193
HIV disease markers						
Years since HIV diagnosis	-0.01	0.345	-0.01	0.856	0.01	0.471
Nadir CD4 (<200 cells/mm3)	0.02	0.841	-0.12	0.828	-0.03	0.657
Diagnosed with AIDS (yes)	-0.04	0.648	-0.29	0.577	-0.03	0.672
On antiretroviral therapy (yes)	-0.16	0.221	-0.86	0.258	-0.02	0.806
Comorbidities						
Hypertension (yes)	-0.15	0.206	-0.76	0.265	-0.01	0.878
Diabetes (yes)	0.28	0.103	1.15	0.256	0.16	0.182
Chronic pulmonary disease (yes)[b]	-0.07	0.681	-0.07	0.951	-0.02	0.844
Cardiovascular disease (yes)[c]	**-0.33**	**0.023**	-1.43	0.088	-0.17	0.088
Current smoker (yes)	0.06	0.517	0.25	0.645	-0.05	0.499
VACS Index						
VACS Index (per 5 points)	**-0.06**	**<0.001**	**-0.25**	**0.003**	**-0.02**	**0.040**
Variance explained by model (r-square)		**0.136**		**0.134**		**0.092**

a NP battery included HVLT-R, Grooved Pegboard and WAIS-R Digit Symbol tests b Asthma, COPD, or Emphysema c Angina, Angioplasty, Bypass surgery, Cardiovascular Accident including stroke, Congestive Heart Failure, Coronary Artery Disease, Myocardial Infarction, or Peripheral Vascular Disease

MOS-COG= Medical Outcomes Study Cognitive Functioning Scale (6 items) CESD=Center for Epidemiological Studies Depression scale (20 items) sRCS- Summary regression-based change score

Findings

- VACS Index score ranged from 0 to 100 (mean=18.4 and median=16).
- In unadjusted analysis: **Higher VACS index score at baseline was associated with a decline in overall NP function over time** (change in overall NP z-score: B= -0.06, p<0.001; change in sRCS: B= -0.03, p=0.009; and change in global T-score: B=-0.27, p=0.001). **This association persisted after adjustment for baseline NP performance, cognitive symptoms, depression, HIV disease markers, medical comorbidities, and demographic variables** (Table 2).
- In adjusted analysis: **Higher VACS index score at baseline predicted a decline in overall NP function** (change in overall NP z-score: B= -0.06, p<0.001; change in sRCS: B= -0.02, p=0.004; and change in global T-score: B= -0.25, p<0.001) (Table 3). **The VACS index score also accounted for a considerable proportion (9% -17%) of the total variances explained by the regression models.**

Conclusions

- Our results replicate findings from the HNRC[4] and suggest that neurocognitive performance is influenced by underlying physiologic injury.
- Interventions to mitigate physiological injury (medical comorbidities) will likely improve neurocognitive function.
- Clinical measures collected as part of routine care may be useful in assessing and managing HIV-associated neurocognitive disorders (HAND).
- The VACS index may be a useful to identify and target those at higher risk for the development of HAND.

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