Asymptomatic Neurocognitive Impairment is Associated with Progression to Symptomatic HIV-associated Neurocognitive Disorders in People with HIV: Findings from the Ontario HIV Treatment Network Cohort Study

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Introduction

Approximately 52% of people with HIV have some form of HIV-associated Neurocognitive Disorder (HAND)[1]

Asymptomatic Neurocognitive Impairment (ANI) is the most common form of HAND and accounts for 70% of all cases[1]

Frascatti's criteria for HAND (Antinori et al. 2007)[2]:

Asymptomatic Neurocognitive Impairment (ANI)
Presence of at least mild neuropsychological impairment in ≥ 2 ability domains AND no decreased everyday functioning

Mild Neurocognitive Disorder (MND)
Presence of at least mild neuropsychological impairment in ≥2 ability domains WITH at least mild decreased everyday functioning

HIV-associated Dementia (HAD)
Overall neuropsychological impairment of at least moderate severity AND "major" functional decline in everyday functioning

- Until very recently, the clinical relevance of ANI diagnosis was limited due to lack of evidence linking ANI with progression to MND or HAD[3]
- A recent study by Grant et al (2014) at the HNRC found that ANI is associated with increased risk (2 to 6 times higher) of progression to symptomatic HAND[4]

Objectives

- **To examine whether ANI is associated with increased risk of progression to symptomatic HAND (i.e., MND or HAD) in Canadians living with HIV**
- **To identify other key determinants associated with change in HAND status.**

Methods

Study participants

Data come from the **Ontario HIV Treatment Network Cohort Study (OCS)**, an observational cohort of people in HIV care in Ontario, Canada. Current analysis includes **679 OCS participants** from the city of Toronto, each of whom completed at least two annual neuropsychological assessments and were neuropsychological normal (NP-N) or ANI at first visit (Table 1).

Neuropsychological functions

- Neuropsychological functioning was assessed annually using a brief battery that included the WAIS-R Digit Symbol[5], WMS-III Spatial Span[6], Grooved Pegboard[7], and Hopkins Verbal Learning Test–Revised[8]
- Raw scores were converted into norm-corrected and practice corrected (test-retest) T-scores using published norms[9-12]
- Global Deficit score (GDS) was computed from T-scores following published guidelines[13]

Cognitive symptoms

Cognitive symptoms/deficits were assessed using the four-item cognitive functioning scale of the Medical Outcomes Study HIV Health survey (MOS-COG)[14,15], which assesses presence and severity of difficulty in memory, attention, reasoning, and concentration functions in the past 4-weeks.

HAND status

HAND status at each visit was determined using the following algorithm constructed by combining Global Deficit Score (GDS) and self-reported cognitive symptoms:

GDS	Self-report cognitive deficit	
	None	One or more
< 0.5	Normal	Normal
0.5 - 2	ANI	MND
>2	HAD	HAD

Additional data

- Self-reported information on demographics and substance use were collected annually using a questionnaire and burden of depressive symptoms were assessed with the Center for Epidemiological Studies-Depression scale (CES-D)[16]
- Data on selected medical comorbidities (i.e., diabetes, hypertension, chronic lung disease, and cardiovascular disease) were extracted from medical records

Statistical analysis

- We used Mann-Whitney U-test or Pearson chi-square tests to compare characteristics of participants at first visit (ANI vs. NP-N). Kaplan-Meier estimates were used to compare ANI and N-PN participants on time to progression to symptomatic HAND.
- Bivariable and multivariable Cox proportional hazards modelling methods were used to estimate risk ratios for earlier progression to symptomatic HAND

Table 1: Sample Characteristics

Characteristics	Total (n=679)	NP-N (n=357)	ANI (n=322)	p-value
Demographics				
Age in years (mean)	45.4	45.0	45.9	0.233
Gender (male)	81%	85%	77%	**0.009**
Race (Caucasian)	62%	65%	59%	0.109
Born in Canada (yes)	57%	59%	56%	0.395
Language spoken at home (English)	84%	88%	80%	**0.003**
Years of education, mean	13.9	13.7	14.1	**0.029**
Employment status (employed)	51%	54%	48%	0.121
HIV Disease markers				
On cART (yes)	83%	80%	87%	**0.023**
Current CD4 count (>500 cells/mm^3)	45%	45%	45%	0.891
Nadir CD4 count (<200 cells/mm^3)	58%	52%	64%	**0.002**
HIV viral load (<50 copies/mL)	72%	69%	76%	0.067
Years since HIV diagnosis (mean)	10.7	10.2	11.2	0.081
Substance Use				
Current smoker	29%	29%	28%	0.802
Non-medicinal drug use[a]	16%	17%	15%	0.430
Alcohol use (AUDIT≥8)[b]	17%	21%	11%	**<0.001**
Comorbidities				
Depression (CESD≥16)	27%	31%	22%	**0.013**
Diabetes	7%	5%	9%	**0.028**
Hypertension	17%	16%	18%	0.546
Chronic pulmonary disease[c]	21%	21%	22%	0.667
Cardiovascular disease[d]	15%	15%	15%	0.812

NP-N, neuropsychological normal
ANI, asymptoatic neuropsychological impairment
cART, combination antiretroviral therapy
AUDIT, Alcohol Use Disorder Identification Test
CESD, Center for Epidemiological Studies – Depression scale

a Past 6 months
b Past 12 months
c Asthma, Chronic Obstructive Pulmonary disease, or emphysema
d Angina, Angioplasty, Bypass surgery, Cardiovascular Accident including stroke, Congestive heart failure, Coronary artery disease, Myocardial infarction, or Peripheral vascular disease

Results

- Among the 679 participants (322 ANI and 357 NP-N), 143 (21%) participants showed progression to symptomatic HAND during the study follow-up period (median follow-up time: 34 months, interquartile range: 20 to 47).
- Participants with ANI status at first visit were more likely than those who were NP-N to show progression to symptomatic HAND (Figure 1).
- Kaplan-Meier estimates (Figure 2) showed that individuals with ANI at first visit had a significantly shorter progression time than those with NP-N (Relative risk: 1.9; 95% CI: 1.33 to 2.61; p<0.001).

Figure 1: HAND status at first visit and progression to symptomatic HAND

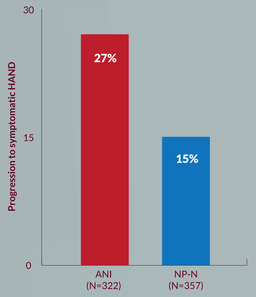
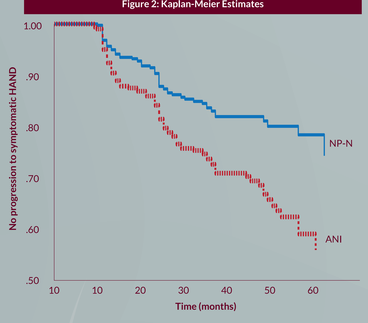


Figure 2: Kaplan-Meier Estimates



Results from a multivariable cox proportional hazards analysis indicated that participants who were ANI at first visit were 1.8 times more likely (95% CI: 1.32 to 2.43) to experience earlier progression to symptomatic HAND than those who were NP-N (Table 2).

Table 2: Predictors of Progression to Symptomatic HAND

Predictor Variable	Univariable model[$] HR	(95% CI)	p	Multivariable Model[$,^] HR	(95% CI)	p
HAND status at baseline						
ANI at baseline [+]	1.73	(1.30, 2.30)	<0.01	**1.79**	**(1.32, 2.43)**	**<0.001**
Demographics						
Age in years [‡]	0.98	(0.97, 0.99)	0.02	1.00	(0.99, 1.02)	0.641
Female [+]	1.68	(1.24, 2.27)	<0.01	**1.58**	**(1.10, 2.27)**	**0.014**
Non-Caucasian [+]	1.68	(1.27, 2.21)	<0.01	1.32	(0.96, 1.83)	0.093
Years of education [+]	0.89	(0.83, 0.95)	<0.01	**0.94**	**(0.88, 0.99)**	**0.037**
Language at home (English) [+]	0.55	(0.39, 0.75)	<0.01	**0.60**	**(0.42, 0.87)**	**0.006**
HIV disease markers						
Recent CD4 (≥500)[‡]	0.64	(0.49, 0.85)	<0.01	0.83	(0.61, 1.13)	0.237
Nadir CD4 (<200) [+]	1.51	(1.12, 2.03)	<0.01	1.10	(0.79, 1.53)	0.379
Viral load (<50)[‡]	0.70	(0.48, 1.02)	0.06	0.72	(0.50, 1.05)	0.089
Substance use/comorbidity						
Current smoker (yes)[‡]	1.82	(1.37, 2.42)	<0.01	**1.73**	**(1.26, 2.39)**	**<0.001**
Depression (CESD ≥ 16)[‡]	2.12	(1.60 2.82)	<0.01	**1.87**	**(1.40, 2.54)**	**<0.001**
Cardiovascular disease [+]	1.52	(1.09, 2.11)	0.01	**1.67**	**(1.15, 2.41)**	**0.007**

[+] Baseline variable
[‡] Time-updated variable
[$] 1,637 observations from 679 individuals were included in analyses
[^] Variables with p<0.10 in bivariable models were included
HR, hazards ratio; **CI**, confidence interval

Other variables independently associated with progression to symptomatic HAND were:

- Female gender
- Fewer years of education
- Lower English proficiency
- Current cigarette smoking
- Higher burden of depressive symptoms
- Cardiovascular disease

Conclusions

1) Asymptomatic Neurocognitive Impairment diagnosis is associated with increased risk of progression to symptomatic HAND (i.e., Mild Neurocognitive Disorder or HIV-Associated Dementia).

2) Regular monitoring (and retesting) of persons with ANI may help to identify those who may progress with neuropsychological impairments.

3) Treatment of cardiovascular risk factors and depression are important avenues for intervention and may delay the onset or progression of HAND.

Strengths: Large sample with supressed HIV viral load; analysis adjusted for several covariates including depressive symptoms, substance use, and nadir CD4; correction for test-retest effects

Limitations: Brief neuropsychological battery and a short cognitive symptoms assessment tool

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