Determinants of Cognitive Impairment in HIV-positive Men on cART and Uninfected Controls

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Background

HIV-positive individuals may be at increased risk of cognitive impairment (CI). Risk factors for CI and the contribution of HIV, antiretroviral treatment, and non-HIV-related factors towards CI remains to be clarified further.

Objectives

To investigate determinants of cognitive impairment.

Methods

The AGE$_h$IV Cohort Study investigates aging-associated comorbidities among HIV-1-infected individuals and highly comparable HIV-uninfected controls, all aged ≥45. HIV-1-infected participants are recruited at the HIV outpatient clinic of the Academic Medical Center in Amsterdam, The Netherlands, and HIV-uninfected controls from the ongoing Amsterdam Cohort Studies on HIV/AIDS and among Amsterdam Public Health Service sexual health clinic attendants. AGE$_h$IV Cohort Study participants were consecutively invited to participate in a nested cognitive substudy. Additional eligibility criteria for the substudy were: male gender, no history of severe neurological disorders, no alcohol abuse or daily illicit drug use, and for the HIV-1-infected group: sustained suppression of HIV viremia on antiretroviral treatment (plasma HIV-RNA <40 copies/mL) for ≥12 months.

103 HIV-1-infected and 75 highly comparable HIV-uninfected participants were enrolled in the cognitive substudy.

They underwent neuropsychological assessment covering six cognitive domains: fluency, attention, information processing speed, executive function, memory, and fine motor function.

CI was diagnosed by 1) Frascati criteria and by 2) multivariate normative comparison (MNC), a novel and likely more accurate technique for evaluating CI (see poster no. 759: Novel Method for More Reliably Estimating the Burden of Cognitive Impairment in HIV).

Multivariable logistic regression was performed to investigate determinants for CI (as defined by Frascati criteria and by MNC).

Acknowledgements

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Demographic and HIV-related characteristics

Data presented as % or median (IQR)	HIV-positives (n=103)	HIV-negatives (n=75)	P-value
Age (years)	52.8 (48.0-60.8)	53.3 (49.0-60.7)	0.65
Men having sex with men (MSM)	93.2%	90.4%	0.50
Dutch origin	86.4%	89.0%	0.60
Known duration of HIV-infection (years)	13.5 (7.4-17.1)	-	-
CD4 count at enrolment (cells/mm^3)	625 (475-800)	-	-
Nadir CD4 count (cells/mm^3)	170 (60-250)	-	-
Duration of undetectable viral load (years)	8.3 (3.5-11.2)	-	-
Duration since start of first ART (years)	11.6 (4.9-14.9)	-	-
ART-naïve at start cART	79.6%	-	-
Prior AIDS	35.0%	-	-

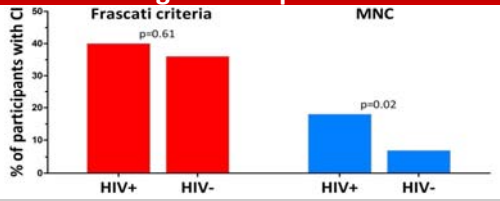
Characteristics related to cognition and behavior

Data presented as % or median (IQR)	HIV-positives (n=103)	HIV-negatives (n=75)	P-value
Dutch as native language	91.3%	94.7%	0.39
Premorbid intelligence (IQ)	102 (95-111)	103 (97-112)	0.29
Depressive symptoms (BDI score) #	4 (2-8)	3 (1-5)	0.09
Use of psychotropic medication	17.5%	13.3%	0.45
Daily to monthly use of ecstasy	1.9%	12.3%	0.01
Daily to monthly use of cocaine	3.9%	4.1%	1.00
Daily to monthly use of cannabis	15.5%	15.1%	1.00
Alcohol intake (units per week)	6 (2-14)	5 (3-12)	0.86
Currently smoking	30.1%	19.2%	0.10
Hypertension*	35.9%	33.3%	0.72

Depressive symptoms were assessed using the Beck Depression Inventory (BDI).

* Hypertension was considered present if diastolic blood pressure ≥90 mmHg and/or systolic blood pressure ≥140 mmHg in three consecutive measurements, and if on antihypertensive medication.

Cognitive impairment



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Multivariable regression model

	Frascati criteria		MNC	
	Odds ratio for CI (95% CI)	P-value	Odds ratio for CI (95% CI)	P-value
HIV infection (y/n)	0.96 (0.50-1.87)	0.91	3.20 (1.10-9.33)	0.03
Premorbid IQ (per 10 ↑)	0.73 (0.56-0.95)	0.02	0.86 (0.61-1.21)	0.39
Native Dutch speaking (y/n)	0.20 (0.05-0.82)	0.03	0.80 (0.17-3.64)	0.77
On psychotropic medication (y/n)	3.24 (1.33-7.88)	0.01	0.51 (0.13-2.05)	0.35
Daily to monthly use of cannabis (y/n)	1.63 (0.64-4.12)	0.30	4.08 (1.41-11.76)	0.01
Hypertension (y/n)	1.87 (0.94-3.71)	0.08	1.28 (0.50-3.29)	0.61

- **The models below, investigating HIV-related determinants, were restricted to the HIV+ studygroup**
- **The models below were adjusted for :**
  -premorbid IQ, native Dutch speaking and use of psychotropic medication (for outcome=CI by Frascati criteria)
  -daily to monthly cannabis use (for outcome=CI by MNC)

Nadir CD4 (per 50 cells/mm^3 ↑)	0.81 (0.67-0.98)	0.03	0.87 (0.69-1.09)	0.23
Soluble CD14# (per 100 ng/mL ↑)	1.09 (1.00-1.18)	0.04	1.12 (1.02-1.23)	0.02

Soluble CD14 is a monocyte activation marker.

Conclusions

- Identification of cognitive impairment was highly dependent on method used.
- Multivariate normative comparison (MNC) which more optimally balances sensitivity and specificity in our hands provided a more reliable estimate of the difference in prevalence between HIV-infected and uninfected participants, when compared to Frascati criteria.
- The likelihood of cognitive impairment as determined by MNC was increased approximately 3-fold in these largely HIV-positive MSM with longstanding virus suppression on cART.
- Amongst those with HIV, after controlling for identified relevant confounders, evidence of increased innate immune activation rather than nadir CD4 was associated with increased likelihood of cognitive impairment.