Neurocognitive Decline in PWH with Virological Response Versus Controls: the ANRS 0093s Aging HAND Study

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BACKGROUND

- Whether people living with HIV (PWH) with virological control experience accelerated neurocognitive performance (NP) decline in comparison with persons living without HIV remains unclear. We assessed 5 year-evolution of NP in PWH and matched controls.

METHODS

- We sequentially included PWH from 6 French clinical centers, aged 55–70 years, with plasma HIV-RNA <50 copies/mL (up to 2 blips allowed) for ≥24 months and a CD4 count ≥200 cells/µL for ≥12 months.
- Volunteers not included if confused, illiterate or non-fluent in French, significant history of brain disease, psychiatric syndromes, sensorial loss, <6 months neurocognitive evaluation, or under tutorship, guardianship, or imprisoned.
- PWH matched for age, sex at birth, and education with controls from the French population-based CONSTANCES cohort. Characteristics collected using standardized questionnaires and neurocognitive tests administered by specifically trained neuropsychologists at enrolment and 5 years later in both populations. Missing values were imputed.
- We assessed NP decline using a Z-score evaluation of five neurocognitive domains with the following tests: Trail Making Test A (TMT-A) (executive function), Verbal semantic fluency Test (VSFT) (language), Wechsler Adult Intelligence Scale-IV (WAIS-IV) (speed of information processing), Finger Tapping Test (FTT) (motor skills), Free and Cued Selective Reminder Test (FCSRT) (episodic memory) and a Global Z-score corresponding to the average of the five tests mentioned above.
- Functional capacities were evaluated with the four items of the Instrumental Activities of Daily Living (IADL) scale.
- We fitted a linear mixed-effects model to account for variability in follow-up duration and adjust for potential confounders.

Table 2: Baseline Z-scores and 5-year Z-scores, and evolution between baseline and second evaluation in PWH and controls (see methods for abbreviations). Adjusted on all common variables in both populations of table 1

Neurocognitive tests	Baseline Z-scores (SEM)		P value difference in baseline Z-score	Evolution of Z-scores between baseline and 5-year(SEM)		ΔZ-score evolution between PWH and controls, [95% confidence interval]	P value difference in Z-score evolution
	PWH	Controls		PWH	Controls		
TMT A	**-0.337 (0.166)**	**0.085 (0.178)**	**0.0005**	-0.314 (0.150)	-0.141 (0.170)	-0.173 [-0.367 ; 0.021]	0.08
VSFT	0.018 (0.162)	0.018 (0.174)	0.99	-0.318 (0.134)	**-0.013 (0.151)**	**-0.305 [-0.481 ; -0.129]**	**0.0007**
WAIS-IV	**-0.988 (0.171)**	**-0.405 (0.184)**	**<0.0001**	-0.155 (0.106)	-0.045 (0.115)	-0.110 [-0.240 ; 0.019]	0.095
FTT	-0.306 (0.173)	-0.408 (0.185)	0.42	-0.364 (0.211)	-0.328 (0.247)	-0.036 [-0.322 ; 0.250]	0.80
FCSRT	-0.234 (0.176)	-0.032 (0.189)	0.12	0.045 (0.161)	0.052 (0.181)	-0.007 [-0.222 ; 0.209]	0.95
Global Z-score	**-0.228 (0.063)**	**-0.094 (0.068)**	**0.004**	-0.124 (0.044)	**-0.063 (0.050)**	**-0.062 [-0.117 ; -0.006]**	**0.03**

PLAIN LANGUAGE SUMMARY: accelerated decline in neurocognitive performance in aged PWH versus matched controls, after taking into account important confounders. Ongoing analysis to evaluate clinical impact of neurocognitive decline

ADDITIONAL KEY INFORMATION
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Increased risk of NP decline in aged PWH compared to well matched controls, after adjusting on confounders, using a global Z-score of neurocognitive performance.

RESULTS

- 204 PWH had neurocognitive baseline evaluation. Median follow-up between first and second NP assessments was 6.81 years (IQR 6.46;7.11) for PWH and 5.01 years (IQR 4.33;5.33) for controls.
- 117 PWH and 585 controls had two neurocognitive evaluations (characterisitics described in table 1). All 117 PWH had virological control at second evaluation.
- At baseline, the adjusted global NP Z-score was significantly lower in PWH compared with controls (ΔZ-score -0.134, 95% CI [-0.226; -0.042], p=0.004), with significant differences observed in the TMT-A, VSFT and the WAIS-IV tests (table 2).
- Global 5-year ΔZ-score decline was significantly greater in PWH versus controls after adjusting for confounders (ΔZ-score evolution between PWH and controls of –0.062, 95% CI [–0.117 to –0.006], p=0.029) (table 2)
- Figure 1 is a Sankey diagram representing evolution of HAND categories in PWH and controls.

Table 1 Variables	PWH (n=117)	Controls (n=585)	P values
Age médian (min, max)	62.5 (55.1 - 70.5)	62.0 (50.5 - 71.5)	0.7
BMI médian (min, max)	24.3 (15.6 - 33.1)	25.8 (15.4 - 46.9)	**<0.001**
Male	97 (83%)	485 (83%)	0.9
Education level			0.9
None	8 (7%)	40 (7%)	
Primary	13 (11%)	65 (11%)	
Secondary	55 (47%)	275 (47%)	
Superior	41 (35%)	205 (35%)	
Hypertension (n=692)	39 (35%)	260 (45%)	**0.05**
MSM (n=638)	55 (51%)	11 (2.1%)	**<0.001**
Hypertriglycemia (n=697)	18 (16%)	37 (6.4%)	**<0.001**
Diabetes (n=685)	11 (9.6%)	50 (8.8%)	0.8
Living alone (n=622)	32 (28%)	35 (7%)	**<0.001**
Smoking status (n=675)			**<0.001**
Never	41 (38%)	230 (41%)	
Passed	42 (39%)	291 (51%)	
ongoing	26 (23%)	45 (8.0%)	
Cannabis (n=661)			**<0.001**
Never	73 (65%)	473 (86%)	
Passed	25 (22%)	69 (13%)	
ongoing	14 (13%)	7 (1%)	
Alcohol consumption (n=683)			**<0.001**
Abstinent	21 (18.9%)	27 (4.7%)	
Moderate	65 (58.6%)	394 (68.9%)	
excessive	23 (20.7%)	123 (21.5%)	
Dependant	2 (1.8%)	28 (4.9%)	
Physical activity (n=674)			0.07
None	28 (25.2%)	97 (17%)	
Moderate	47 (42.4%)	230 (41%)	
Intensive	36 (32.4%)	236 (32%)	
Renal insufficiency (n=693)			**<0.001**
DGF ≥ 90	34 (29%)	247 (43%)	
60–89	73 (62%)	317 (55%)	
30–59	10 (9%)	12 (2%)	
Depression (n=657)	29 (27%)	56 (10%)	**<0.001**
Hyperchosterolemia (n=690)	52 (45%)	261 (45%)	0.9
Cardiovasculair disease (n=686)	17 (15%)	23 (4.0%)	**<0.001**
Lymphocytes T CD4, median (IQR)	663 (495 - 790)	NA	
Lymphocytes T CD4/T CD8	0.88 (0.60 - 1.33)	NA	
Nadir CD4 count (min, max)	180 (105-267)	NA	

DISCUSSION

- Increased risk of NP decline in aged PWH compared to well matched controls, using a global Z-score.
- NP changes primarily concerned asymptomatic neurocognitive impairment (ANI), followed by minor neurocognitive disorder (MND) in cortical and subcortical domains, and NP fluctuated in both populations, particulalrly for ANI.
- Strengths: well-matched multicentric cohort of aged PWH and controls, long-term follow-up, standardized procedures and analysis including social determinants of health
- Limits : lack of adjustment on anxiety or use of psychotropic drugs
- Ongoing analysis: if increased decline in global z-score in PWH versus controls translates into significant clinical impact using different neurocognitive classifications.

CONCLUSION

- **HIV status is a factor of NP decline, even in PWH with controlled viremia.**
- **NP decline affected executive functions.**
- **ANI fluctuation, potentially reflecting oversentivity of the Frascati classification.**
- **Our study underscores the need to assess NP in aging PWH, and to manage all modifiable factors of impairment decline.**

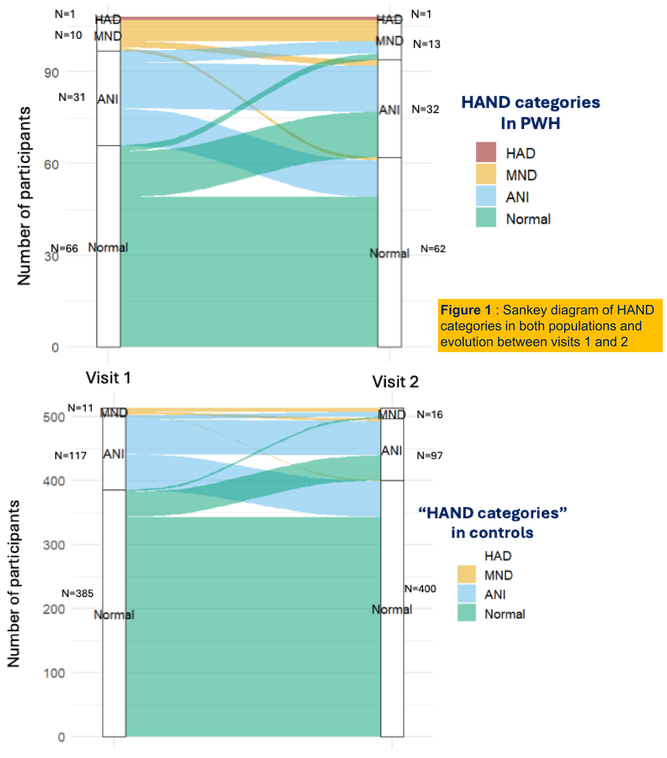


Figure 1 : Sankey diagram of HAND categories in both populations and evolution between visits 1 and 2