Cognitive disorders in HIV-infected patients: are they HIV-related?

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Objectives: Large unselected studies on representative samples of HIV-infected patients with a whole battery of neuropsychological tests and cerebral MRI scan are required to assess the frequency of neurocognitive impairment (NCI), the determinants of mild neurocognitive disorders (MNDs), or HIV-associated dementia (HAD) and the relationship between NCI and MRI scan findings.

Methods: Investigation of 400 consecutively enrolled HIV-1-infected adults from the ANRS CO3 Aquitaine Cohort, using standardized neurocognitive tests chosen to achieve consistency with Frascati's criteria. Half of the patients had a cerebral MRI scan allowing gray and white matter volume measurement. Factors associated with NCI were studied by logistic regression models.

Results: Median age of participants was 47 years, 79% were male and 89% received combination antiretroviral treatment (cART), of whom 93% had plasma HIV RNA below 500 copies/ml. Median CD4 cell count was 515 cells/μl. Prevalence of NCI was 59%, including 21% of asymptomatic NCI, 31% of MND, and 7% of HAD. A low level of education, prior neurologic AIDS-defining disorders event, anxiety, depressive symptoms, and prior history of brain damage were independently associated with MND or HAD, but neither HIV nor cART-related variables. The presence of NCI was significantly associated with lower gray matter fraction.

Interpretation: In this large unselected cohort, a high prevalence of symptomatic neurocognitive disorders was mainly related to its traditional determinants and associated with gray matter atrophy at early stages of the disease.

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Introduction

More than 15 years after combination antiretroviral therapy (cART) became available and despite a dramatic decrease of AIDS-specific neurologic complications, neurocognitive impairment (NCI) is common and currently represents a major case management issue in patients living with HIV. When the 2007 criteria of the American Association of Neurology were applied, studies reported an overall prevalence of NCI ranging between 22 and 55% [1–5]. However, these estimates have been based on very specific study populations that had either reached an advanced stage of immunosuppression or had a long-standing suppressed viremia. Indeed, these patients were usually assessed after cART changes or already expressed cognitive complaints, which limited the extrapolation of results to a broader spectrum of patients in care in resource-rich countries.

Studying NCI in HIV-infected patients remains quite relevant as such disorders may negatively affect adherence to treatment, daily life activities and employment, and be associated with AIDS occurrence, progression to dementia, and poor survival [6–11]. NCI may also limit physical activities, and have important consequences on quality of life [3,12].

The causes and underlying mechanisms of NCI remain poorly understood. Apart from its traditional determinants, that is older age, low education level, and cardiovascular risk factors, some studies have also suggested an association with HIV-related characteristics, such as the most recent T-CD4 lymphocyte count (CD4) as well as the CD4 nadir, the level of HIV replication, or the type of cART [5,13–16]. Finally, data are sparse regarding the brain structure in the context of NCI. Few studies performed on too few patients have found reduced subcortical volumes and metabolite abnormalities in HIV-infected patients on cART [17,18]. More recent studies have found an association between CD4 nadir and cerebral atrophy [19], but large studies evaluating the association between NCI (according to the 2007 definition) and cerebral structural gray and white matter volumes are missing. Large-scale comprehensive cohort-based studies are still needed in order to perform these investigations.

We aimed at estimating the prevalence of NCI and exploring the determinants of symptomatic NCI in a large and unselected cohort of HIV-infected patients in care. Cerebral gray and white volumes were also measured with conventional 3D T1 MRI scans in a subgroup to assess the relationship between NCI and cerebral volumes.

Patients and methods

Patients

The Agence Nationale de Recherche contre le Sida et les hépatites virales (ANRS) CO3 Aquitaine Cohort is a prospective hospital-based cohort of HIV-1-infected patients under routine clinical management in South-Western France. This cohort was initiated in 1987 at the Bordeaux University Hospital and in four other public hospitals by the Groupe d'Epidémiologie Clinique du Sida en Aquitaine (GECSA). All adult in-patients or out-patients of the participating hospital wards who had an HIV-1 infection confirmed by western blot testing, at least one follow-up visit after enrollment or a documented date of death, and who provided an informed consent were eligible for inclusion. A standardized questionnaire containing data from different categories: epidemiological (age, sex, HIV-transmission category), clinical events since last medical contact whether or not HIV-related, laboratory (HIV-RNA, T-CD4 lymphocyte count, hemoglobin, hepatitis B and C serological status), and therapeutic (antiretrovirals, prophylaxis, and others) was recorded by physicians and research nurses at each contact. All events were coded according to the International Classification of Diseases 10th revision (ICD10) [20].

Patients from the Aquitaine Cohort were consecutively enrolled in this special survey assessing cognitive disorders, between June 2007 and November 2009, in five clinics of the Bordeaux University Hospital until the target of 400 study participants was reached. They were eligible if they were 18 and over, and out-patients were in stable medical condition without acute medical events requiring immediate care, treatment change, or hospitalization. Those who agreed underwent an MRI scan measure of gray and white matter volumes. The overall study was approved by the Biomedical Ethics Committee of the Bordeaux district ('CPP du Sud-Ouest et Outre Mer III'), and written informed consent was obtained from all participants. The study procedures were in accordance with the standards of Ethics Committee and with the Helsinki Declaration.

All participants completed first a clinical examination, blood sampling, and collection of detailed medical history regarding brain and cardiovascular events, as well as history of substance use and professional activity. A psychiatric-oriented interview was then performed with an evaluation of current mood and affective disorders. The administration of special questionnaires captured self-reported cognitive complaints and instrumental activities of daily living (IADLs). Finally, cognitive testing was performed as described below. At last, according to Letendre *et al.* [21], each antiretroviral drug was given a central nervous system (CNS) penetration effectiveness (CPE) score between 1 (low CNS penetration) and 4 (high CNS penetration) and a regimen total calculated for the ongoing antiretroviral cART at the time of the study.

Neuropsychological testing

Neuropsychological testing was performed by trained psychologists according to standardized procedures. It

included the following list of tests and measurements exploring seven ability domains designed to achieve consistency with standardized definition of HIV-associated NCI: the trail making test (parts A and B) assessing attention and mental flexibility (Reitan 1979); the digit symbol substitution task assessing psycho-motor speed (Wechsler 1981); the backwards digit span task assessing working memory (Miller 1956); the free and cued selective reminding test assessing encoding and retrieval abilities in verbal episodic memory (Grober and Buschke 1987); the Isaacs set test (Isaacs and Kennie 1973) and verbal fluency task assessing semantic and phonemic fluency; the Rey Osterrieth Complex Figure Test assessing visuo-constructive abilities (copy) and visual memory (retrieval) (Osterrieth 1944); and finally the Purdue Pegboard Test assessing manual dexterity and coordination (Fleishman and Ellison 1962).

Self-reported cognitive difficulties in everyday life were assessed using a short cognitive complaint scale. Functional abilities in IADLs were assessed with the Lawton and Brody Scale [22], to which an item regarding timetable management was added. Information was also recorded on tobacco and alcohol consumptions, use of intravenous and other drugs, and use of any medication. The Center for Epidemiologic studies-Depression (CES-D) scale was used to assess depressive symptomatology (with recommended cut-off score of $\geq$17 in men and $\geq$23 in women to identify depressive symptomatology), as well as the anxiety item of the Mini International Neuropsychiatric Interview (MINI).

The presence of NCI was defined according to the 2007 revised research criteria for HIV-associated neurocognitive disorders [5]. Briefly, asymptomatic neurocognitive impairment (ANIs) were defined by a test score at least 1 SD below the mean of demographically adjusted normative scores using US norms in at least two ability domains, without any symptoms. Mild neurocognitive disorder (MND) was defined by a score of at least 1 SD below the mean of demographically adjusted normative scores in at least two different ability domains along with mild interference in daily functioning in the absence of dementia. Finally, the cognitive pattern compatible with the diagnosis of HIV-associated dementia (HAD) was defined by a score of at least 2 SDs below the mean of demographically adjusted normative scores in at least two different cognitive domains, along with marked difficulty in coping with activities of daily living due to cognitive impairment.

In the same study period, participants underwent standardized locomotor tests assessing balance (Berg Balance scale, One leg standing, Functional Reach test), overall locomotion capacity (Six-minute-walk test, Timed-up-and-go test), and lower limb muscle performance [Five-times-sit-to-stand test (5STS)]. Poor test performance was defined by cut-offs based on age-specific data of the general population. Detailed method and results of the locomotor assessments were recently reported elsewhere [23]. In brief, the by far most frequently altered locomotor test was the 5STS test, with 53% of the study participants having test result of more than 2 SDs from the expected age-specific mean in the general population.

Laboratory assessments

Diabetes was defined by at least two glycemia above 7 mmol/l during follow-up or by any use of antidiabetic drug(s). High cholesterol was defined by a plasma cholesterol greater than 6.24 mmol/l on at least two consecutive measures or any use of lipid-lowering drugs; high triglycerides were defined by a plasma level above 2.2 mmol/l at two consecutive measures or any use of lipid-lowering drugs. Chronic hepatitis C was defined by the presence of hepatitis C serum antibodies and chronic hepatitis B by the presence of hepatitis B surface antigen.

MRI acquisition and analysis

Brain MRI examination was proposed to all study participants without contraindications for MRI with the aim to include approximately 50% of the participants in the MRI assessment. In transverse plan, an anatomical high-resolution 3D Magnetization Prepared RApid Gradient Echo T1-weighted sequence (repetition time = 8.5 ms, echo time = 4 ms, flip angle = matrix size = 256×256, field of view = 256 mm to cover the whole brain, 170 slices of 1 mm, resulting in a voxel dimension of $1 \times 1 \times 1\,mm^3$) was performed using a 1.5 Tesla Intera system (Philips Medical Systems, Best, The Netherlands).

An optimized Voxel-Based Morphometry (VBM) procedure, using unified segmentation and normalization approach on SPM5, was used to extract gray and white matter volumes for each patient [24,25]. Each MRI scan was visually inspected so as to discard segmentation failure. Head size variability between patients was accounted for in statistical analysis by using relative gray or white matter brain volumes using the following formulae: [gray matter volume/total intracranial volume (TIV)] $\times$ all patient TIV mean (with TIV = gray matter volume + white matter volume + cerebrospinal fluid volume).

Statistical analysis

Differences between subgroups were assessed by χ^2 test or Fisher's exact test for categorical variables, and by Student's *t*-test or Wilcoxon test for continuous variables. Estimates of the prevalence of cognitive disorders were calculated with their binomial 95% confidence interval (CI).

Univariable and multivariable logistic regression analyses were performed to explore determinants of symptomatic NCI, as defined by the presence of either MND or HAD.

Multivariables analyses of determinants of symptomatic NCI were developed using different steps: variables with a

P value less than 0.25 in univariable analyses were selected, and then studied using two different specific multivariable models: the first one included only HIV-infection-related variables (transmission group, AIDS stage, HIV-RNA, CD4, cART), the other one included only other characteristics unrelated to HIV infection (demographic, cardiovascular, neurological, and psychological variables). Variables were selected using a backward stepwise procedure (threshold $P < 0.25$). The final multivariable model was built from the remaining variables in the two previous models, using the same backward strategy, but with a threshold of *P* less than 0.05. The construction of the multivariable model was restricted to the subset of the initial sample with no missing data on any variable of interest, apart from CD4 nadir, for which a dummy variable was used to indicate replacement of missing values. Thus, 369 patients (i.e. 92.3% of the initial sample) were considered in multivariable analyses. All statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

Characteristics of the study sample

Out of 3655 patients under active follow-up in the Aquitaine Cohort, 3025 were seen at the participating sites of the University Hospital of Bordeaux during the study period and 400 were included in this substudy special survey on cognitive and locomotor disorders. Characteristics of the participants compared to the remaining 2625 patients under active follow-up in the participating sites from the ANRS CO3 Aquitaine Cohort in 2007 are shown in Table 1. Study participants tended to be more frequently male, older, homosexuals, on cART, virologically suppressed, and presenting with hypercholesterolemia than the remaining of the cohort.

Cognitive and locomotor test results

Neurocognitive impairment was observed in 234 out of the 400 participants, yielding a prevalence of 58.5% (95% CI 53.5–63.4%), including 83 patients with ANI]20.8% (95% CI 16.9–25.1)], 124 with MND [31.0% (95% CI 26.5–35.8)], and 27 with HAD [6.7% (95% CI 4.5–9.7)].

A total of 229 participants among 390 with available data (59%) had at least one cognitive complaint. Among them, 62% had NCI detected on cognitive tests. Among patients with no cognitive complaint, 57% had NCI detected on cognitive tests.

Three hundred and nineteen patients had also undergone standardized locomotor tests [19]. A significant association was found between cognition and poor lower limb muscle performance: 58% of patients with NCI also had poor lower limb muscle performance evaluated by the

Table 1. Characteristics of the study participants ($n = 400$) and of the patients under active follow-up in the entire ANRS CO3 Aquitaine Cohort, 2007–2009.

Characteristic	Study participants ($n = 400$)	Other patients under active follow-up in the participating sites* ($n = 2625$)	*P*-value
Sex: men (%)	79	72	$<10^{-2}$
AIDS stage (%)			0.52
No AIDS stage	76	79	
AIDS stage (except for neuro AIDS)	19	16	
Neuro AIDS	5	5	
History of cardiovascular event (%)	3.5	4.1	0.58
Hypercholesterolemia** (%)			$<10^{-2}$
Hypercholesterolemia (with use of lipid-lowering drugs)	19	18	
Hypercholesterolemia (with no use of lipid-lowering drugs)	25	18	
No hypercholesterolemia	56	64	
HIV transmission group (%)			$<10^{-3}$
Intravenous drug use	15	16	
Homosexuals (except for i.v. drug use)	48	38	
Heterosexual/other	37	46	
Hepatitis B co-infection** (%)	7	7	0.94
Hepatitis C co-infection** (%)	22	24	0.51
On antiretroviral treatment (%)	89	85	0.01
Current HIV-1 RNA level <500 copies/ml (%)	85	79	0.02
Median age (years, IQR)	47 (42–53)	44 (39–50)	$<10^{-4}$
Median time since HIV diagnosis (years, IQR)	12.6 (6.4–17.9)	12.7 (6.8–17.9)	0.79
Median CD4 nadir (cells/μl, IQR)**	260 (154–385)	261 (162–377)	0.86
Median current CD4 cell count (cells/μl, IQR)	515 (350–700)	501 (349–687)	0.63

IQR, interquartile range.
*Patients under active follow-up in 2007 in the ANRS CO3 Aquitaine Cohort at the University Hospital of Bordeaux who were not included in the cognitive study.
**Missing data for: hypercholesterolemia ($n = 16$), hepatitis B co-infection ($n = 160$), hepatitis C co-infection ($n = 203$), CD4 nadir ($n = 602$).

5STS test vs. 46% of those with no NCI ($P=0.04$). When we considered patients with symptomatic NCI only (MND and HAD), 63% of them had poor 5STS test performance vs. 47% of patients without symptomatic NCI ($P=0.004$).

Factors associated with symptomatic neurocognitive impairment (mild neurocognitive disorder or HIV-associated dementia)

The 369 patients included in the regression models were not statistically different from patients with missing data, with regards to the majority of the variables of interest, but were more often professionally inactive (46 vs. 26%; $P=0.03$) and had more often hypertriglyceridemia (53 vs. 27%; $P=0.006$).

Patients with symptomatic NCI (defined by MND and HAD) significantly differed from those without symptomatic NCI others in terms of age, education level, professional activity, history of cardiovascular event, hypercholesterolemia, any history of CNS disease, anxiety, depressive symptoms, and prior neurologic AIDS-defining disorders (neuroAIDS) event. By contrast, there was no association between symptomatic NCI and HIV characteristics, namely transmission group, duration of infection, current CD4 cell count and nadir, HIV RNA, and hepatitis co-infections (Table 2). In the univariate analysis, patients with MND/HAD tended to be less frequently treated with efavirenz (17.7 vs. 10.6%; $P=0.06$) and had a longer history of zidovudine treatment ($P=0.02$). Type of cART [protease inhibitor vs. non-nucleoside reverse transcriptase inhibitor (NNRTI) vs. protease inhibitor + NNRTI vs. other combinations] was not associated with any neurocognitive endpoints ($P=0.51$) as well as the CPE score (median = 7 in patients without MND/HAD vs. 6 in patients with MND/HAD; $P=0.83$). The association between age and symptomatic NCI was not linear. When age was treated as a categorical variable, it was not associated with NCI in univariable comparisons

In the final multivariable model, characteristics that remained independently associated with symptomatic NCI were: history of neuroAIDS event, lower level of education, anxiety, depressive symptoms, and any history of brain damage (Table 3).

When the analysis was restricted to the sample of patients without anxiety, depressive symptoms or history of brain damage, and with a high education level (high school or educational school) only 36 patients among 192 (18.8%) had symptomatic NCI. When further restricting to patients without history of cardiovascular comorbidity (history of cardiovascular event, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, smoking, and chronic kidney disease), only three patients among 31 (9.7%) had symptomatic NCI. When we analyzed separately the group of patients with ANI, we did not find any factor associated with the risk of ANI (data not shown).

MRI results

Two hundred and fifteen patients were included in the MRI study. After exclusion of images with major acquisition artifacts or poor quality segmentation and patients with cerebral injury or missing neuropsychological data, 178 patients were included in the subsequent analysis. Patients included in the MRI study were older than patients who did not (49.0 vs. 46.4 years), more frequently male (86 vs. 74%), and less frequently drug users (4 vs. 10%). There were no statistical differences between the two groups of patients regarding the other variables studied.

Compared to patients without NCI, patients with NCI (either ANI, MND, or HAD) had a significantly lower gray matter volume [650.9 (95% CI 639.7–662.1) vs. 627.3 (95% CI 614.8–639.9); $P=0.006$]. After exclusion of 14 patients with neuroAIDS events or CNS injury, gray matter volume remained significantly lower in patients with NCI than in other patients [635.67 (95% CI 574.91–695.31) vs. 653.67 (95% CI 605.67–701.67); $P=0.03$].

There was a trend for decreasing gray matter volumes across categories of NCI with more similar results for asymptomatic and minor cognitive disorders as compared to HAD. Opposite trends were observed for cerebrospinal fluid volumes (Table 4).

Discussion

In this large survey among HIV-infected outpatients, we found a high prevalence of NCI (58.5%), including ANI, MND, and HAD, according to the criteria of the American Association of Neurology [5]. Most of the cases were related to non-HIV-related determinants in this population harboring biomarkers showing a good control of HIV infection and stable medical condition. This observation resembles those of the newly diagnosed cases of the 2007 report of the revised research criteria for HIV-associated neurocognitive disorders [5]. Our prevalence estimates fall in the same range as recent studies in Europe, Australia, and North America, although the latter were conducted in a more selected group of patients [26–28]. By contrast, our study sample was fairly representative of the overall Aquitaine cohort and comparable to other HIV-infected populations in France with, in particular, a high proportion of patients treated with cART and controlled infection (>500 CD4 cells/μl and undetectable HIV RNA) [29]. It is likely that the methods and the population studied may account for the small differences observed in the different studies published so far. However, the high prevalence of NCI documented in

Table 2. Patients' characteristics according to cognitive performance ($n = 400$), ANRS CO3 Aquitaine Cohort, 2007–2009.

Characteristics	No cognitive impairment or ANI ($n = 249$)		MND or HAD ($n = 151$)		P
Median age (years, IQR)	46	(41–52)	48	(42–56)	0.02
Sex: men (*n*, %)	201	(80.7)	116	(76.8)	0.35
Transmission group: (*n*, %)					0.11
i.v. drug use	31	(12.5)	29	(19.2)	
Homosexuals (except for i.v. drug use)	127	(51)	64	(42.4)	
Heterosexual/other	91	(36.5)	58	(38.4)	
Hepatitis B co-infection (*n*, %)*	17	(7.1)	11	(7.4)	0.89
Active hepatitis C co-infection (*n*, %)*	21	(8.6)	21	(14.2)	0.09
AIDS stage (*n*, %)					
No AIDS stage	202	81.1	103	68.2	$<10^{-2}$
AIDS stage (except for neuroAIDS)	41	16.5	34	22.5	
NeuroAIDS	6	2.4	14	9.3	
Education level high school (*n*, %)	146	(58.6)	55	(36.4)	$<10^{-4}$
Technical school (*n*, %)	88	(35.3)	73	(48.3)	
No diploma (*n*, %)	15	(6.0)	23	(15.2)	
Professional activity (*n*, %)	162	(65.1)	59	(39.1)	$<10^{-4}$
Inactive or retired (*n*, %)	87	(34.9)	92	(60.9)	
Median time since HIV diagnosis (years, IQR)	12	(6–17.5)	13.5	(9–18)	0.10
Median CD4 nadir (cells/μl, IQR)*	263	(158–374)	258	(151–385)	0.46
Median CD4 cell count (cells/μl, IQR)	506	(357–692)	531	(335–712)	0.80
Current HIV RNA level <500 copies/ml (*n*, %)	211	(84.7)	127	(84.1)	0.86
History of cardiovascular event (*n*, %)	5	(2)	9	(6)	0.04
Diabetes (*n*, %)*	22	(8.9)	17	(11.3)	0.44
Hypertension (*n*, %)*	47	(19.0)	32	(21.3)	0.58
Hypercholesterolemia (*n*, %)*	99	(39.9)	76	(50.3)	0.04
Hypertriglyceridemia (*n*, %)*	118	(47.6)	84	(55.6)	0.12
Any cardiovascular comorbidity (cardiovascular event, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, smoking, chronic kidney disease) (*n*, %)	208	(83.5)	139	(92.1)	0.01
Any history of cerebral event (stroke, brain trauma, neurologic disease) (*n*, %)	39	(15.7)	46	(30.5)	$<10^{-3}$
Depressive symptoms (*n*, %)*	47	(18.9)	63	(42.0)	$<10^{-4}$
Anxiety (*n*, %)*	35	(14.1)	59	(39.3)	$<10^{-4}$
Any psychologic disease (depressive symptoms, anxiety, dysthymia) (*n*, %)	69	(27.7)	91	(60.3)	$<10^{-4}$
Substance dependence (*n*, %)	31	(12.4)	26	(17.2)	0.19
Type of current antiretroviral treatment (*n*, %)					0.51
No treatment	27	(10.8)	16	(10.6)	
Current PI and NNRTI-based cART	14	(5.6)	7	(4.6)	
Current PI-based cART (without any NNRTI-based cART)	123	(49.4)	80	(53.0)	
Current NNRTI-based cART (without any PI-based cART)	60	(24.1)	27	(17.9)	
Other type of current ARV treatment	25	(10.1)	21	(13.9)	
On efavirenz (*n*, %)	44	(17.7)	16	(10.6)	0.06
History of zidovudine treatment	174	(69.9)	121	(80,1)	0.02
Median CPE score	7	(5–7)	6	(5–8)	0.83

ANI, asymptomatic neurocognitive impairment; cART, combination antiretroviral therapy; CPE, central nervous system penetration effectiveness; HAD, HIV-associated dementia; i.v., intravenous; MND, minor neurocognitive impairment; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q1–Q3, first quartile to third quartile.

*Missing data for: hepatitis B co-infection ($n = 11$), active hepatitis C co-infection ($n = 9$), diabetes ($n = 1$), hypertension ($n = 3$), hypercholesterolemia ($n = 1$), hypertriglyceridemia ($n = 1$), depressive symptoms ($n = 2$), anxiety ($n = 1$), CD4 nadir ($n = 47$ in no cognitive impairment or ANI group, $n = 30$ in MND or HAD group).

the present study raises numerous questions in this population with well controlled HIV infection, suggesting that other, non-HIV-related factors may contribute to this impairment. The CNS HIV Antiretroviral Therapy Effects Research study recently found a slightly lower prevalence of NCI (52%) in a large cohort of HIV-infected patients. However, we believe that the health condition of this population was poorer since they were much more frequently at the AIDS stage and only 40% of them had undetectable plasma HIV RNA in plasma [28]. In a selected group of patients with undetectable viral load, the Swiss Cohort found a higher prevalence of HIV-associated neurocognitive disorders (HANDs) with 84% among patients with cognitive

Table 3. Factors associated with symptomatic neurocognitive disorders, multivariable models, ANRS CO3 Aquitaine Cohort, 2007–2009.

	Separate multivariable models				Complete multivariable model			
	Initial model		Final model		Initial model		Final model	
Characteristic ($n=369$)	Odds ratio	*P*	Odds ratio	[95% CI]	Odds ratio	*P*	Odds ratio	[95% CI]
HIV-infection-related variables								
AIDS stage								
No AIDS stage	1	0.013	1		1	0.032	1	
AIDS stage (except for neuroAIDS)	1.41		1.37	[0.79;2.37]	1.34		1.53	[0.86;2.75]
NeuroAIDS	5.15		4.72	[1.62;13.8]	4.46		4.87	[1.59;14.9]
On efavirenz treatment (yes vs. no)	0.70	0.28	0.68	[0.35;1.30]	0.76	0.46		
Transmission group								
i.v. drug use	1.32	0.37	1.36	[0.72;2.56]	1.18	0.66		
Homosexuals (except for i.v. drug use)	0.79		0.80	[0.49; 1.28]	0.86			
Heterosexual/others	1		1		1			
History of zidovudine treatment (yes vs. no)	1.63	0.12	1.63	[0.94;2.80]	1.13	0.69		
CD4 nadir (cells/μl)∗								
>350	1	0.56						
[200;350[	0.64							
<200	0.73							
Active hepatitis C co-infection (yes vs. no)	1.03	0.94						
Time since HIV diagnosis (years)		0.47						
<7	1							
[7;12]	0.78							
[12;17]	1.33							
>17	0.99							
Non HIV-infection-related variables								
Education level								
High school	1	0.001	1		1	0.008	1	
Technical school	2.21		2.21	[1.34;3.65]	1.99		2.16	[1.31;3.55]
No diploma	3.18		3.18	[1.34;7.54]	2.94		3.39	[1.48 ;7.80]
History of cardiovascular event (yes vs. no)	2.35	0.201	2.35	[0.63;8.75]	2.02	0.32		
Hypercholesterolemia (yes vs. no)	1.37	0.23	1.37	[0.82;2.29]	1.35	0.28		
Hypertriglyceridemia (yes vs. no)	1.45	0.15	1.45	[0.87;2.43]	1.32	0.30		
Dysthymia disorder (yes vs. no)	1.64	0.15	1.64	[0.83 ;3.22]	1.70	0.13		
Generalized anxiety (yes vs. no)	2.33	0.006	2.33	[1.28;4.26]	2.47	0.004	2.93	[1.67;5.14]
Depressive symptoms (yes vs. no)	2.13	0.01	2.13	[1.20;3.81]	1.89	0.036	2.11	[1.23;3.63]
Alcohol dependence (yes vs. no)	2.01	0.11	2.01	[0.84;4.81]	2.17	0.08		
Any history of neurological disease except for neuroAIDS – stroke, brain trauma, neurologic disease-(yes vs. no)	2.16	0.008	2.16	[1.22;3.81]	2.12	0.011	2.05	[1.18;3.58]

complaints and 64% among noncomplainers [26]. In a selected group of patients with CD4 cell count above 350 cells/μl, the Strategies for Management of Antiretroviral Therapy (SMART) study found a prevalence of NCI of 51% [27]. The high prevalence of NCI observed in our cohort was neither associated with incomplete viral suppression nor current or nadir CD4 cell count. Furthermore, we did not find any association either with the current cART regimen or with the CPE score.

We found that other conditions are over-represented in HIV-infected patients as compared to the general population, and may explain the very large majority of symptomatic cognitive disturbances. Indeed, the

Table 4. Association between global cerebral volume (MRI) and stage of neurocognitive impairment. Aquitaine Cohort, 2007–2009.

	No NCI ($N=76$)	Asymptomatic neurocognitive disorders ($N=42$)	Minor neurocognitive disorders ($N=54$)	HIV-associated dementia ($N=6$)	*P*-value
White matter volume (cm^3) (mean, SD)	499.7 (36.1)	494.7 (46.4)	494.9 (33.5)	492.7 (38.7)	0.755
Gray matter volume (cm^3) (mean, SD)	650.9 (49.1)	628.6 (62.2)	627.7 (65.4)	615.4 (71.0)	0.098
Cerebrospinal fluid volume (cm^3) (mean, SD)	585.5 (71.9)	612.8 (93.6)	613.4 (73.5)	627.9 (97.3)	0.135

multivariate analysis showed that determinants associated with symptomatic NCI were a low education level, anxiety, depression, and any history of brain damage. Regarding HIV-infection-related variables, only neuroAIDS remained associated with NCI. When we considered the nonsymptomatic NCI (ANI), we did not find any variable associated with the risk of ANI in this population. However, we believe that the low number of cases in this category may limit the power of this specific analysis.

Lastly, we must underline that among patients with no cognitive complaint, 57% had NCI detected on cognitive tests suggesting that risk factors for NCI could serve the purpose of identifying a group of patients who could benefit from proactive screening and intervention.

The HAND classification criteria may often be very difficult to apply in clinical practice in determining if observed neurocognitive problems can be attributed to HIV disease.

A history of neurologic event or psychiatric disturbance as assessed by the CES-D and MINI was reported in 234 patients (58.5%). Furthermore, 374 patients out of 400 (93.5%) had a history of cardiovascular event or were exposed to cardiovascular risk factors, a major condition for increasing the risk of NCI in the general population [30]. However, since we could not demonstrate an independent association with cardiovascular comorbidity, further studies are required to explore NCI in HIV-infected patients as a potential consequence of accelerated vascular ageing.

The MRI data collected in a subsample of our patients show that the quantity of gray matter was lower in patients with NCI. Cerebral atrophy is a common finding in HIV-infected patients with cognitive impairment and has been described before and after the widespread use of antiretrovirals [19,31]. Our study shows for the first time in a large sample a strong association between a reduced volume of gray matter and any stage of NCI. Such results are important for a better understanding of the nature of HIV-associated neurocognitive disorders since they suggest that the cognitive deficits observed in HIV-infected patients are not only due to functional changes in neural circuitry but could be the consequence of macrostructural brain lesions [32]. Since we did not find any association between HIV-related variables and NCI, it may be hypothesized that macrostructural brain lesions may be related to comorbid conditions rather than to HIV itself. Recently, studies of HIV-associated neurocognitive disorders conducted in patients mostly treated with cART have shown a limited association with immune activation and viral replication [26,28]. The role of antiretrovirals themselves is still difficult to assess and conflicting results are reported in the literature. It is clear that cART dramatically decreases the incidence of AIDS dementia [33]. Numerous publications have also shown that cART improves neurocognitive functioning [34]. On the contrary, high rates of NCI persist at all stages of HIV infection in the cART era; some studies have found that treatment interruption was associated with neuropsychological improvement and that antiretrovirals with good CNS penetration were associated with poorer cognitive performance [35,36]. In the present study, we did not find any association in the multivariable analysis between type of cART or CPE score and the risk of NCI. Even if the cross-sectional design of the study may explain the lack of association, we suggest that in patients treated for a long time, the effect of CPE score vanished with more powerful antiretroviral regimens associated with plasma viral load control as has been observed in neuroAIDS patients [37].

Interestingly, we found a strong association between NCI and poor lower limb muscle performance as reflected by the results of the 5STS test. Given that performance in the balance tests was satisfactory in the large majority of participants [23], we hypothesize that poor 5STS performance in HIV-infected patients is primarily attributable to muscle function and not necessarily to central nervous manifestations. Common risk factors may explain the association between NCI and 5STS performance, but this speculation requires further investigation in a longitudinal study.

The association between NCI and poor lower limb muscle performance may increase the risk of functional disability and result in limitations in daily living activities. The aging of the HIV-infected population may thus result in an increasing frequency of dependency and thus, preventive measures should be evaluated.

The impact of other preventive measures for cognitive impairment such as screening for anxiety or depression and control of modifiable cardiovascular risk factors has not been fully evaluated so far. We have shown in univariable analyses that cardiovascular disease was associated with poor neurocognitive performance, as it was also the case in other recent studies. The SMART group recently found that prior cardiovascular disease, and also hypertension and hypercholesterolemia were associated with NCI in a substudy of 292 patients [27]. With an increasing life expectancy and a particularly high prevalence of cardiovascular risk factors in HIV-infected patients, the pattern of cerebrovascular damage may increase in the near future whatever the study population.

Finally, the anxiety and depression symptoms are highly prevalent in HIV-infected patients and their relationship with cognitive performance is already well known in the general population [38]. Thus, screening for cognitive impairment should be accompanied by screening for depression.

Taken together, our findings suggest that, in patients that are well controlled for HIV infection, cardiovascular and psychiatric diseases, in addition to any history of brain damage including neuroAIDS, and low level of education are related to NCI, and that such neuropsychological deficits are associated with reduced cerebral gray volume. These results have to be confirmed in a further large longitudinal study that we are implementing with the patients included in the present study. From a clinical point of view, screening for cognitive impairment should be accompanied by screening for cardiovascular and psychiatric comorbidities, in particular, depression and anxiety disorders. The results gathered from the MRI substudy showing that macrostructural brain lesions are present even in patients with ANIs are of particular concern. Since cognitive intervention strategies are still to be developed in this population, other preventive measures including a strict control of cardiovascular risk factors, and the screening and treatment of anxiety and depression, in addition to HIV RNA replication control, are urgently required to decrease the burden of cognitive disorders in HIV-infected patients.

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Conflicts of interest

The authors declare to have no conflict of interest.

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