Cross-sectional analysis of cognitive function using multivariate normative comparisons in men with HIV disease

Zheng Wang[a], Samantha A. Molsberry[c], Yu Cheng[a,b], Lawrence Kingsley[d,e], Andrew J. Levine[f], Eileen Martin[g], Cynthia A. Munro[h,i], Ann Ragin[j], Leah H. Rubin[i,k], Ned Sacktor[i], Eric C. Seaberg[k], James T. Becker[l,m,n], for the Neuropsychology Working Group of the Multicenter AIDS Cohort Study

Background: Prevalence estimates of cognitive impairment in HIV disease vary widely. Here we used multivariate normative comparison (MNC) with identify individuals with impaired cognition, and to compare the results with those using the Frascati and Gisslén criteria.

Methods: The current project used data collected before October 2014 from bisexual/gay men from the Multicenter AIDS Cohort Study. A total of 2904 men (mean age 39.7 years, 52.7% seropositive) had complete data in six cognitive domains at their first neuropsychological evaluation. *T*-scores were computed for each domain and the MNC was applied to detect impairment among seronegative and seropositive groups.

Results: The MNC classified 6.26% of seronegative men as being impaired using a predetermined 5% false discovery rate. By contrast, the Frascati and the Gisslén criteria identified 24.54 and 11.36% of seronegative men as impaired. For seropositive men, the percentage impairment was 7.45, 25.73, and 11.69%, respectively, by the MNC, Frascati and Gisslén criteria. When we used seronegative men without medical comorbidities as the control group, the MNC, the Frascati and the Gisslén criteria identified 5.05, 27.07, and 4.21% of the seronegative men, and 4.34, 30.95, and 4.48% of the seropositive men as having cognitive impairment. For each method, serostatus was not associated with cognitive impairment.

Conclusion: The MNC controls the false discovery rate and therefore avoids the low specificity that characterizes the Frascati and Gisslén criteria. More research is needed to evaluate the sensitivity of the MNC method in a seropositive population that may be sicker and older than the current study sample and that includes women.

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[a]Department of Statistics, [b]Department of Biostatistics, University of Pittsburgh, Pittsburgh, Pennsylvania, [c]Population Health Sciences, Harvard University, Cambridge, Massachusetts, [d]Department of Epidemiology, [e]Department of Infectious Diseases and Microbiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, [f]Department of Neurology, David Geffen School of Medicine, UCLA, Los Angeles, California, [g]Department of Psychiatry, Rush University School of Medicine, Chicago, Illinois, [h]Department of Psychiatry, [i]Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, [j]Department of Radiology, Northwestern University, Evanston, Illinois, [k]Department of Epidemiology, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, Maryland, [l]Department of Psychiatry, [m]Department of Neurology, and [n]Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

Correspondence to James T. Becker, PhD, Department of Psychiatry; Department of Neurology; Department of Psychology, University of Pittsburgh, 3501 Forbes Avenue, Suite 830, Pittsburgh, PA 15213, USA.

Tel: +1 412 246 6970; e-mail: beckerjt@upmc.edu

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Introduction

Since the beginning of the HIV epidemic, it has been clear that the nervous system, and in particular cognitive and neurological functions, can be negatively affected. Immediately after infection, there can be a period of an aseptic meningitis [1–3] that persists for a short period of time and responds well to medication [4,5]. In the 1980s and early 1990s, a substantial proportion of individuals with HIV disease developed significant cognitive and neurological changes that ranged from what was then referred to as minor cognitive motor disorder to AIDS dementia complex (ADC) [6]. With the use of combination antiretroviral therapy starting in 1996 the incidence of ADC (later termed HIV-associated dementia, or HAD) declined significantly; however, there remained a persistence of milder forms of cognitive impairment [7].

Estimating the prevalence of neuropsychological impairment due to HIV, collectively called HIV-associated neurocognitive disorders (HAND), is controversial, with the rates of HAND varying widely across studies. The 'Frascati' criteria [8] tend to result in a higher rate of cognitive dysfunction than more stringent revised criteria (Gisslén) [9]. Indeed, within the Multicenter AIDS Cohort Study (MACS) prevalence estimates of any degree of impairment could be as high as 25% *regardless* of whether an individual was seropositive.

One of the difficulties of using either of these criteria is that there is a high false discovery rate (FDR). That is, these methodologies tend to classify individuals without HIV disease, and who are thus presumed to be 'healthy' with respect to their cognitive functions, as being impaired. Even the revised criteria, that uses a more stringent cutoff for impairment in individual cognitive domains, fails to account for correlations among different cognitive domain scores, which also affect the FDR. To address the problem of the FDR, a new method was developed called multivariate normative comparisons (MNC) [10] which is useful for identifying individuals with cognitive impairment while at the same time controlling the FDR.

The current method has been applied to individuals with HIV disease drawn from the AGE_HIV Cohort Study [11], where the rates of cognitive impairment based on the two standard criteria were compared with the rate of impairment using the MNC. That study found that the MNC improved the detection of cognitive impairment among seropositive individuals while controlling the FDR in the seronegative control group. Among the seronegative individuals, the Frascati criteria resulted in highest rate of neuropsychological impairment (36%), followed by the revised Gisslén criteria at a lower overall impairment rate, while the MNC maintained the FDR at 5% and identified a higher proportion of seropositive individuals who were cognitively impaired. Similar analysis has also been done to Pharmacokinetic and Clinical Observations in PeoPle Over fiftY cohort study [12]. They found that global deficit score (GDS), Frascati and MNC identified, respectively, 26, 20, and 5% of the control group as having cognitive impairment, suggesting low specificity of the GDS and Frascati methods. Simulation studies showed that, without controlling for intercorrelation among cognitive domains, cognitive impairment classification methods solely based on counting abnormal domains or averaging all domain scores will have concerns of inflated FDR or decreased power [13].

The purpose of the present analysis is to replicate and extend these findings among men participating in the MACS. In addition to detailed evaluations of cognitive functions, the study also provides information on multiple medical, biological, immunological, and behavioral factors that could affect neuropsychological test performance. To that end, we identified all participants who did not have any of a large number of comorbid conditions that might have an impact on cognitive functions – so-called healthy participants [14]. We first used all seronegative participants to compute normative values that were used in the analysis, then repeated the same analysis but used only the healthy participants without comorbid conditions in the seronegative group as the healthy control. Thus, the goal of the current analysis was to compare rates of cognitive impairment as a function of serostatus and the presence of comorbidities across all three classification methodologies.

Methods

Participants and study design

Six thousand, nine hundred and seventy-two ($N = 6972$) gay or bisexual men were recruited into the MACS from four sites – the University of Pittsburgh, the University of California Los Angeles, Northwestern University, and the Johns Hopkins University [15,16]. These men enrolled in the study during three time periods: 4954 enrolled in

1984/1985, 688 enrolled in 1987/1995, and 1350 men enrolled in 2001/2003. Enrollment criteria includes at least 18 years old; sexual relationship with at least five partners in the past 5 years; seronegative, or seropositive without clinical AIDS before HAART, or seropositive with $CD4^+$ cell count and viral load known within 6 months before HAART initiation. The data used for this analysis were gathered on or before 30 September 2014.

Each individual enrolled in the MACS completed neuropsychological testing; initially, this was semiannual. In 2005, this schedule was changed so that every participant was evaluated biannually, unless their performance was judged as impaired, in which case it was repeated semiannually. Those individuals over the age of 65 were evaluated on an annual basis. More details about MACS study enrollment have already been described [17,18].

Standard protocol approval, registration, and patient consent

The MACS was reviewed and approved by each institution's Institutional Review Board, and all participants signed written statements of Informed Consent prior to initiation of any research procedures.

Assessments

Comorbidities

The database was scanned for the presence of comorbidities that might have a negative impact on neuropsychological test performance [14,19–24]. These comorbidities included factors such as central nervous system disorders, brain structural lesions, tuberculosis, tumors, cardiovascular diseases, cocaine and alcohol abuse, leukoencephalopathy, hepatitis C, impaired hearing and vision, movement problems, infectious disease, malnutrition, and liver problems. Top 10 comorbidities observed in our study are nonparalytic poliomyelitis, affective psychoses, ischemic heart disease, myocardial infarction, angina pectoris, peripheral neuropathy, liver disease and cirrhosis, heart failure, renal failure, and emphysema.

Neuropsychological tests at first classification

The battery of neuropsychological tests covered six domains of cognitive function including, working memory/attention, motor speed/coordination, executive functioning, learning, memory, and speed of information processing (Supplemental Table 1, http://links.lww.com/QAD/B510). For each of these cognitive domains, a *T*-score was calculated based on the model developed in the seronegative participants [18]. The *T*-scores were adjusted for education, age, and race, and standardized to a mean of 50 and a SD of 10. A summary of domain *T*-scores was obtained by averaging all available test scores in each domain, with the exception of the motor domain where the lower of the Grooved Pegboard scores was used instead [17]. A careful review of the data revealed that some of the *T*-scores were unusually small or large values.

Cognitive impairment classification criteria

To be classified as having neuropsychological impairment using the Frascati criteria, an individual participant must have two or more *domain* scores 1 SD below the mean. To be classified as impaired using the Gisslén revised criteria, an individual participant must have two or more domain *T*-scores 1.5 SD below the mean.

These two standard methods examine each domain score separately. However, the MNC method computes a single measure of distance between an individual participant's domain scores and the 'normative' mean of the seronegative participants across all domains. The method then compares the distance using the threshold that is determined by a prespecified FDR. The distance measure is called Hotelling's T^2, which is analogous to a multivariate version of Student's *t* test and which follows an *F*-distribution. The MNC method accounts for the variability in each of the domain scores as well as the intercorrelations among the various domain scores. The threshold is specifically chosen *a priori* and any distance beyond this threshold is deemed abnormal. To be classified as cognitively impaired using this methodology, a participant's *T*-scores should also be below the means of the healthy controls across all domains. For this cross-sectional analysis, we used a one-sided test with an alpha of 5% for the MNC method which results in a specificity of 95%.

Statistical analysis

We used data from the first neuropsychological visit from the men who had all the domain scores available. All participants were screened for extreme score values, and extreme domain scores were truncated at 4 SDs below or above the mean. It was of interest to see how participants differ in demographics and baseline characteristics by serostatus; we first compared seropositive and seronegative men using two-sample *t* tests for continuous variables and chi-squared tests for categorical variables, and reported effect sizes using Cohen's *d* for continuous variables and Cohen's *h* for categorical variables [25]. To compute the MNC statistic and the thresholds that we used for the Frascati and the Gisslén criteria, we first obtained the sample means of all the six domain scores and the covariance matrix from all the seronegative individuals who were treated as 'healthy controls'. To identify cognitive impairment within reference group, we implemented a 'jackknife' technique where all the 'healthy controls' except the one to be tested is used as the reference group.

As noted above, the seronegative group also contained men with comorbidities which may have affected their test performance. Thus, the seronegative volunteers were separated into those who did not *ever* have comorbidities

during the study and those who ever had *any* comorbidities. We then applied these three sets of criteria for cognitive impairment to each participant, comparing their cognitive functioning scores to the normative means in reference to the underlying variability, both measured from the seronegative men who did not have any comorbidities. Similar analyses were performed for seropositive men by their impairment status, again using seronegative individuals without comorbidities as the reference group. Chi-squared test was used to test cognitive impairment rate difference as a function of comorbidity among seropositive individuals.

In addition to reporting the estimated proportion of individuals with cognitive impairment in each group using these three criteria, we also included agreement rates between two criteria, which represents the proportion of individuals flagged as the same cognitive statuses by two criteria. Confidence intervals (CIs) were also obtained for impairment rates by each criterion and the pairwise agreement rates. More specifically, we drew 10 000 bootstrap samples (sampling with replacement from the total sample) and, for each bootstrap sample, estimated the percentage of cognitive impairment for each group. A 95% CI was obtained based on the 2.5 and 97.5th percentiles of these bootstrap estimates.

Some participants did not have information on comorbid conditions and were treated as a separate group when only seronegative men without comorbidities were used as healthy controls. We compared demographic and baseline characteristics of these participants to those without comorbidity information. We also compared the men included in study and those excluded from study when both groups lacked information on comorbidities. We also compared men included in study and men with HIV-infection by cognitive impairment status from the MNC. Differences in rates of impairment were examined as a function of viral suppression status, AIDS and calendar time (before/after 1996). Again, two-sample *t* tests and Chi-squared tests were used for continuous and categorical variables respectively for group comparisons, and Cohen's *d* and *h* were reported as effect sizes for continuous and categorical variables, respectively. All the statistical analyses were conducted in 3.4.1 (R Core Team, Vienna, Austria).

Results

First, we observed that 28 participants had *T*-scores below 10 for the motor speed/coordination domain, and their scores were truncated at 10, and one participant had a *T*-score above 90 for the speed of information processing domain, which was truncated at 90. The truncated sample met the multivariate normal distribution assumption.

Comparisons between seropositive and seronegative men are shown in Table 1. HIV-infected men were younger, had less high blood pressure, lower $CD4^+$ T-cell count, reported less use of alcohol use but more current tobacco smoking, use of illicit drugs, and injection drug use, were more likely to be non-white, had greater depressive symptoms and fatigue, had poorer social functioning (interfered by physical or emotional health), more insomnia, poorer general health, fewer years of education, lower income, younger age, and lower scores in information processing speed domain as compared with seronegative men.

We first report impairment rates by each of the three classification criteria using the entire group of seronegative men as healthy controls ($n = 1373$). The Frascati criteria identified 337 seronegative individuals (24.54%, 95% CI: 23.07–26.13%) and 394 of the seropositive men (25.73%, 95% CI: 22.70–28.90%) as being cognitively impaired. The Gisslén criteria identified 156 seronegative men (11.36%, 95% CI: 10.07–12.38%) as having a cognitive impairment compared with 179 of the seropositive men (11.69%, 95% CI: 9.88–13.74%). After setting the FDR at 5%, the MNC categorized 86 seronegative men (6.26%, 95% CI: 5.26–7.37%) and 114 of the seropositive men (7.45%, 95% CI: 6.14–9.40%) as cognitively impaired. None of these methodologies identified significantly different rates of cognitive impairment as a function of serostatus (*P* values: Frascati 0.63, Gisslén 0.82, MNC 0.18).

We also calculated the rate of agreement among all men between the Frascati and Gisslén criteria at 86.36% (95% CI: 84.95–87.67%), between the MNC and Gisslén criteria at 89.84% (95% CI: 88.74–91.22%), and that between the Frascati and MNC criteria at 78.89% (95% CI: 77.34–80.54%). Any pair of the three methods showed significant differences in the rates of cognitive impairment.

We repeated the analyses using the group of seronegative men with no significant comorbidities as the 'healthy' reference group; the rates of impairment, the CIs around these rates, and the rates of agreement between the various criteria are shown in Table 2 and Fig. 1. Again, there were no statistically reliable differences among the rates of impairment as a function of serostatus (all *P* values >0.17), though all three classification methods categorized slightly higher proportions of men in the seropositive group compared with the seronegative group. Among seropositive participants, no significant difference was found between those with and without comorbidities (*P* value $= 0.35$).

Supplemental Table 2, http://links.lww.com/QAD/B510, shows the characteristics of the men in the study as a function of whether or not information regarding comorbidities was available. Those men who did not have such information were less educated, older, more likely to

Table 1. Comparison between seropositive and seronegative participants.

	All (2904)	HIV− (1373)	HIV+ (1531)	*P* value	Cohen's *d/h*
Age	39.70 ± 9.83 (2904)	40.99 ± 11.10 (1373)	38.55 ± 8.38 (1531)	<0.001	0.25
Non-white	30.82% (2904)	26.22% (1373)	34.94% (1531)	<0.001	0.092
>12 Years education	80.72% (2904)	84.56% (1373)	77.27% (1531)	<0.001	0.12
High blood pressure	33.52% (2094)	38.77% (957)	29.11% (1137)	<0.001	0.10
Diabetes	19.49% (1180)	20.38% (579)	18.64% (601)	0.49	0.018
Dyslipidemia	73.52% (1216)	71.60% (588)	75.32% (628)	0.16	0.055
Current alcohol use	38.85% (2904)	41.10% (1373)	36.82% (1531)	0.021	0.046
Current illicit drug use[a]	48.50% (2876)	44.49% (1360)	52.11% (1516)	<0.001	0.087
Drug with needle	4.75% (2866)	3.61% (1356)	5.76% (1510)	0.009	0.022
No. of $CD4^+$ positive cells	725.07 ± 381.43 (2839)	970.46 ± 333.65 (1338)	506.33 ± 272.84 (1501)	<0.001	1.53
Depression (CESD)	11.40 ± 10.60 (2818)	10.44 ± 10.15 (1336)	12.27 ± 10.92 (1482)	<0.001	0.17
Cognitive domains					
Motor	46.89 ± 10.53 (2904)	46.97 ± 10.57 (1373)	46.82 ± 10.50 (1531)	0.70	0.014
Executive	49.95 ± 9.44 (2904)	50.16 ± 9.31 (1373)	49.76 ± 9.55 (1531)	0.26	0.042
Speed	49.71 ± 8.77 (2904)	50.22 ± 8.83 (1373)	49.25 ± 8.69 (1531)	0.003	0.11
Learn	49.69 ± 9.33 (2904)	49.83 ± 9.20 (1373)	49.57 ± 9.45 (1531)	0.46	0.028
Memory	49.88 ± 9.48 (2904)	49.93 ± 9.33 (1373)	49.84 ± 9.61 (1531)	0.79	0.010
Working memory	49.24 ± 9.18 (2904)	49.43 ± 9.37 (1373)	49.08 ± 9.02 (1531)	0.31	0.038
Fatigue often[b]	25.11% (1346)	20.57% (632)	29.13% (714)	<0.001	0.088
Poor social functioning[c]	11.14% (1346)	8.07% (632)	13.87% (714)	0.001	0.058
Poor general health[d]	19.38% (1347)	12.50% (632)	25.45% (715)	<0.001	0.13
Individual gross income ≥50 000	24.75% (1826)	30.56% (818)	20.04% (1008)	<0.001	0.11
Emotionally unstable[e]	16.42% (1346)	14.40% (632)	18.21% (714)	0.070	0.039
Current smoking	38.14% (2863)	34.08% (1347)	41.75% (1516)	<0.001	0.083
Insomnia	30.71% (1501)	24.09% (739)	37.14% (762)	<0.001	0.14

Percentage (%) is shown for categorical variable. Mean ± SD is computed for continuous variable. Number of participants having such a variable with nonmissing data is displayed in parenthesis. CESD, center for epidemiologic studies depression scale.
[a]Including marijuana, cocaine, heroin, and uppers.
[b]Fatigue level is averaged by scores for full of pep, energy, worn out, and tiredness, ranging from 0 (fatigue all the time) to 100 (not at all), and fatigue often is defined to have mean score less than 50.
[c]Social functioning is averaged by scores for social activities and amount of social time interfered by physical/emotional health, ranging from 0 (extremely poor) to 100 (not at all), and poor social health is defined to have mean score less than 50.
[d]General health is averaged by scores for health level and self-health assessments, ranging from 0 (extremely poor) to 100 (excellent), and poor general health is defined to have mean score less than 50.
[e]Emotional well being is averaged by scores for nervous and depressive level, calmness and happiness, ranging from 0 (none of the time) to 100 (all of the time), and emotionally unstable is defined to have mean score less than 50.

be non-white, and they had consistently lower scores in all six neuropsychological domains. This last finding is consistent with the high rate of cognitive impairment that was found in these individuals regardless of which of the classification schemes were used.

Supplemental Table 3, http://links.lww.com/QAD/B510, summarizes the characteristics of the men as a function of whether or not they had information on comorbidities. Those included in study while lacking comorbidities information had less alcohol use, more $CD4^+$ cell count, less proportion of white and less fatigue, and were older.

In Table 3, we compare the characteristics of all the 2904 men in the study as a function of their cognitive

Table 2. Cognitive impairment classification results (seronegative without comorbidities as healthy control reference group).

	Seronegative, *n* = 1373			Seropositive, *n* = 1531		
	No comorbidities, *n* = 713	Comorbidities, *n* = 309	Missing info, *n* = 351	No comorbidities, *n* = 714	Comorbidities, *n* = 359	Missing info, *n* = 458
MNC						
N (%)	36 (5.05%)	22 (7.12%)	194 (55.27%)	31 (4.34%)	21 (5.85%)	236 (51.53%)
95% CI	3.59–6.38%	4.12–10.42%	49.54–65.08%	2.85–6.54%	3.86–9.62%	45.16–57.64%
Frascati						
N (%)	193 (27.07%)	103 (33.33%)	331 (94.30%)	221 (30.95%)	114 (31.75%)	401 (87.55%)
95% CI	24.23–29.07%	27.53–39.27%	91.60–96.60%	27.04–35.39%	25.41–37.43%	84.40–90.53%
Gisslén						
N (%)	30 (4.21%)	18 (5.83%)	304 (86.61%)	32 (4.48%)	18 (5.01%)	353 (77.07%)
95% CI	2.12–5.66%	2.66–10.09%	81.84–90.30%	2.04–7.22%	2.13–8.36%	72.73–81.72%

Agreement among all participants between the Frascati and Gisslén criteria is 79.06% (95% CI: 77.55–80.61%), between the MNC and Gisslén criteria is 85.37% (95% CI: 84.02–87.02%), and between the Frascati and MNC criteria is 68.97% (95% CI: 67.36–71.28%). CI, confidence interval; MNC, multivariate normative comparison.

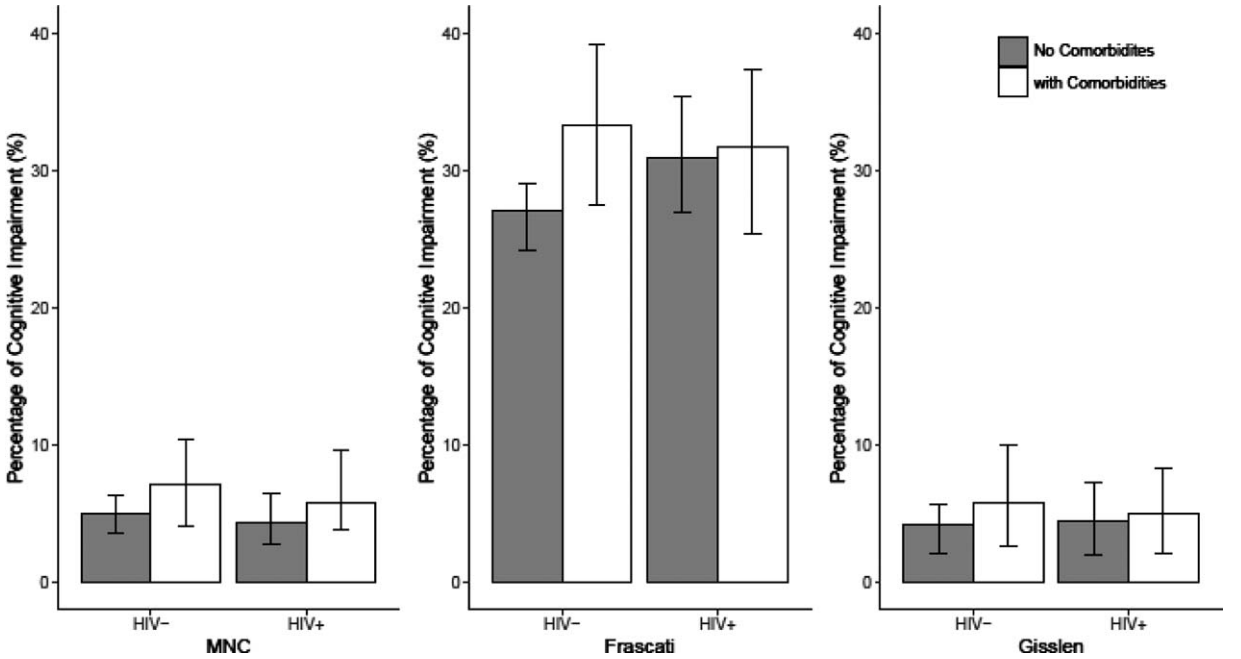

Fig. 1. Cognitive impairment classification results (seronegative without comorbidities as healthy control reference group).

Table 3. Comparison between cognitively impaired and not impaired participants by multivariate normative comparison (seronegative without comorbidities as healthy control reference).

	Impaired, $n = 540$	Not impaired, $n = 2364$	*P* value	Cohen's *d*/*h*
Age	41.65 ± 10.47 (540)	39.26 ± 9.63 (2364)	<0.001	0.24
Non-white	39.44% (540)	28.85% (2364)	<0.001	0.11
>12 Years education	73.52% (540)	82.36% (2364)	<0.001	0.14
High blood pressure	35.08% (400)	33.13% (1675)	0.49	0.021
Diabetes	16.02% (256)	20.45% (924)	0.13	0.045
Dyslipidemia	72.01% (268)	73.95% (948)	0.58	0.028
Current alcohol use	30.45% (532)	40.75% (2364)	<0.001	0.11
Current illicit drug use[a]	44.76% (534)	49.36% (2342)	0.061	0.052
Drug with needle	6.78% (531)	4.28% (2335)	0.020	0.025
No of $CD4^+$ positive cells	702.20 ± 367.71 (524)	730.24 ± 384.35 (2315)	0.12	0.074
Depression (CESD)	12.79 ± 11.38 (524)	11.08 ± 10.39 (2294)	0.002	0.16
Cognitive domains				
Motor	38.43 ± 15.01 (540)	48.82 ± 8.06 (2364)	<0.001	1.07
Executive	41.79 ± 11.32 (540)	51.82 ± 7.84 (2364)	<0.001	1.17
Speed	42.46 ± 8.97 (540)	51.37 ± 7.83 (2364)	<0.001	1.10
Learn	41.40 ± 10.14 (540)	51.59 ± 8.01 (2364)	<0.001	1.21
Memory	41.55 ± 10.00 (540)	51.79 ± 8.25 (2364)	<0.001	1.19
Working memory	45.28 ± 10.42 (540)	50.15 ± 8.63 (2364)	<0.001	0.54
Fatigue often[b]	26.48% (287)	24.74% (1059)	0.60	0.018
Poor social functioning[c]	14.98% (287)	10.10% (1059)	0.026	0.049
Poor general health[d]	22.53% (288)	18.79% (1059)	0.34	0.028
Individual gross income ≥50 000	19.73% (370)	26.03% (1456)	0.015	0.065
Emotionally unstable[e]	17.42% (287)	16.15% (1059)	0.67	0.013
Current smoking	40.56% (535)	37.59% (2328)	0.22	0.032
Insomnia	31.61% (329)	30.46% (1172)	0.74	0.012

Percentage (%) is shown for categorical variable. Mean ± SD is computed for continuous variable. Number of participants having such a variable with nonmissing data is displayed in parenthesis. CESD, center for epidemiologic studies depression scale.
[a]Including marijuana, cocaine, heroin, and uppers.
[b]Fatigue level is averaged by scores for full of pep, energy, worn out, and tiredness, ranging from 0 (fatigue all the time) to 100 (not at all), and fatigue often is defined to have mean score less than 50.
[c]Social functioning is averaged by scores for social activities and amount of social time interfered by physical/emotional health, ranging from 0 (extremely poor) to 100 (not at all), and poor social health is defined to have mean score less than 50.
[d]General health is averaged by scores for health level and self-health assessments, ranging from 0 (extremely poor) to 100 (excellent), and poor general health is defined to have mean score less than 50.
[e]Emotional well being is averaged by scores for nervous and depressive level, calmness and happiness, ranging from 0 (none of the time) to 100 (all of the time), and emotionally unstable is defined to have mean score less than 50.

Table 4. Comparison between cognitively impaired and not impaired among seropositive participants by multivariate normative comparison (seronegative without comorbidities as healthy control).

	Impaired, $n=288$	Not impaired, $n=1243$	P value	Cohen's d/h
Age	40.26 ± 9.36 (288)	38.16 ± 8.09 (1243)	<0.001	0.25
Non-white	45.14% (288)	32.58% (1243)	<0.001	0.14
>12 Years education	69.79% (288)	79.00% (1243)	0.001	0.14
High blood pressure	30.57% (229)	28.74% (908)	0.64	0.019
Diabetes	14.07% (135)	19.96% (466)	0.16	0.060
Dyslipidemia	73.45% (147)	75.88% (481)	0.63	0.036
Current alcohol use	26.50% (283)	39.19% (1235)	<0.001	0.13
Current illicit drug use[a]	49.82% (285)	52.64% (1231)	0.43	0.033
Drug with needle	7.45% (282)	5.37% (1228)	0.23	0.021
No. of $CD4^+$ positive cells	503.83 ± 284.30 (280)	506.90 ± 270.26 (1221)	0.87	0.011
Depression (CESD)	14.36 ± 11.90 (279)	11.78 ± 10.63 (1203)	<0.001	0.24
Cognitive domains				
Motor	37.98 ± 14.63 (288)	48.87 ± 8.00 (1243)	<0.001	1.13
Executive	41.47 ± 11.80 (288)	51.68 ± 7.78 (1243)	<0.001	1.18
Speed	42.22 ± 9.05 (288)	50.88 ± 7.74 (1243)	<0.001	1.08
Learn	41.15 ± 9.87 (288)	51.52 ± 8.19 (1243)	<0.001	1.21
Memory	41.32 ± 10.19 (288)	51.81 ± 8.31 (1243)	<0.001	1.21
Working memory	45.10 ± 9.89 (288)	50.00 ± 8.54 (1243)	<0.001	0.56
Fatigue often[b]	30.19% (159)	28.83% (555)	0.82	0.014
Poor social functioning[c]	18.87% (159)	12.43% (555)	0.052	0.065
Poor general health[d]	28.13% (160)	24.68% (555)	0.44	0.026
Individual gross income ≥50 000	19.12% (204)	20.27% (804)	0.79	0.012
Emotionally unstable[e]	22.01% (159)	17.12% (555)	0.20	0.050
Current smoking	41.12% (287)	41.90% (1229)	0.86	0.009
Insomnia	38.95% (172)	36.61% (590)	0.64	0.025

Percentage (%) is shown for categorical variable. Mean ± SD is computed for continuous variable. Number of participants having such a variable with nonmissing data is displayed in parenthesis. CESD, center for epidemiologic studies depression scale.
[a]Including marijuana, cocaine, heroin, and uppers.
[b]Fatigue level is averaged by scores for full of pep, energy, worn out, and tiredness, ranging from 0 (fatigue all the time) to 100 (not at all), and fatigue often is defined to have mean score less than 50.
[c]Social functioning is averaged by scores for social activities and amount of social time interfered by physical/emotional health, ranging from 0 (extremely poor) to 100 (not at all), and poor social health is defined to have mean score less than 50.
[d]General health is averaged by scores for health level and self-health assessments, ranging from 0 (extremely poor) to 100 (excellent), and poor general health is defined to have mean score less than 50.
[e]Emotional well being is averaged by scores for nervous and depressive level, calmness and happiness, ranging from 0 (none of the time) to 100 (all of the time), and emotionally unstable is defined to have mean score less than 50.

classification using the MNC methodology, regardless of their serostatus. As a group, the impaired men were less likely to use alcohol, or injection drugs. They were older, less likely to be white, and reported more symptoms of depression than the unimpaired men, and they had less education, lower income, and had poorer social function. As would be predicted, they had consistently lower scores in all six neuropsychological domains.

Finally, Table 4 shows characteristics of the seropositive men as a function of cognitive status using the MNC methodology. Those classified as having cognitive impairment by the MNC had less alcohol use, a lower proportion of whites, more symptoms of depression, lower cognitive scores across all six domains and were less educated and older. Among the seropositive participants, there was no significant difference in cognitive impairment rates as a function of viral suppression (cognitively impaired 22.90%, $n=345$, among virally suppressed participants; 19.12%, $n=633$, among those not virally suppressed; P value $=0.19$; $h=0.039$). Of critical importance is the observation that the rate of impairment is higher among individuals with AIDS (cognitively impaired 27.27%, $n=77$, in AIDS group; 18.36%, $n=1454$, in no-AIDS group; P value $=0.072$; $h=0.092$), but lower among individuals tested prior to 1996 (cognitively impaired 15.68%, $n=746$, prior to 1996; 22.84%, $n=785$, on or after 1996; P value <0.001; $h=0.073$), or who were part of the initial enrollment cohorts.

Discussion

The data reported here replicate and extend prior investigations of the relative merits of using MNC methodologies to determine the rates of impairment among individuals with and without HIV disease. Unlike other studies, we did not find a specific relationship between HIV infection and cognitive impairment regardless of the methodology utilized [26]. In addition, characteristics of the men as a function of their cognitive classification suggests that there may be significant cohort differences that may explain the paradoxical observation that while individuals with AIDS are *more* likely to be impaired, those who were examined prior to 1996 were *less* likely to be impaired.

With regard to the MNC methodology we believe this procedure may be superior to the alternative consensus criteria that do not, by design, consider the intercorrelations among the cognitive domain scores. That is, the MNC method is able to control the FDR – which is set *a priori* – in a way that is not possible using the Frascati or Gisslen criteria. These latter two methods attempt to control the FDR by setting a higher threshold for 'impairment' while the MNC is able to do that empirically. In the current study, we have the advantage that cognitive impairment in an otherwise healthy group of individuals is relatively unlikely. Thus, even setting the FDR at 5% may be overestimating the true rate of impairment among our control volunteers.

Unlike other reports, we did not find a consistent difference in the rate of cognitive dysfunction among the seropositive men [26]. However, when we look back at the prior history of the MACS cohort, we had previously reported that 'HIV-related cognitive changes typically occur with the onset of constitutional symptoms or AIDS-defining illness. Before the appearance of severe illness, cognitive impairment is no more common among seropositive than seronegative individuals' [15]. Our finding that the rate of abnormality was significantly higher among the seropositive men with AIDS is consistent with this earlier observation from prior to the use of almost any pharmacotherapy (e.g. azidothymidine).

The results of this analysis also suggest that there may be a previously unidentified difference as a function of cohort of entry that has a significant impact on the group-level analysis of rates of impairment. It is important to remember that early in the MACS neuropsychological substudy not all of the men were enrolled [27]. In addition, the absence of effective pharmacotherapy during the early days of the epidemic meant that there were significant limitations as to which of the seropositive men were able to attend the research clinic and spend time doing the neuropsychological testing. Once effective therapy became available, even those men who had had an AIDS-defining illness might nevertheless be physically able to come to the clinic and complete the assessment. If this were the case, it might help to explain why we have both a higher rate of impairment among our men with AIDS as well as a higher rate of impairment among those men whose first neuropsychological assessment was in 1996 or thereafter.

Although it is beyond the scope of this article, death is a significant competing risk for cognitive impairment among men enrolled in the study and tested prior to 1996. At that time ADC was associated with a high mortality rate and survival of only approximately 6 months after diagnosis [2]. Further, if AIDS-defining illnesses other than ADC (e.g., pneumocystis pneumonia, wasting syndrome) also reduced the probability that a volunteer would attend a study visit, then we would be unaware of their cognitive status at that time. On the contrary, most longitudinal studies, including our own, and especially those that are attempting to compare and contrast rates of impairment across the history of the epidemic pay little attention to factors such as these. Competing risk, legacy effects, and sampling biases can have a major impact on the outcomes of interest, and consequently have a major impact on healthcare policy.

There are several limitations to this study. First, only men were included in the MACS, and the seropositive population in this study was relatively healthy, as about 67% of seropositive participants did not have any comorbidities (714 men vs. 359 men), which is similar to 70% seronegative participants who did not have any comorbidities (713 vs. 309). Second, a large proportion of participants did not have information on comorbidity, among whom we observed a higher impairment rate. Those men who had comorbidities may have a higher impairment rate than those who did not have any comorbidities, if we had the information on every participant. Lastly, as we did not have detailed clinical ratings, the Frascati classification that was used in our study may be different from the one used in the CHARTER study [28], which was another large study of cognition. Thus, our results cannot be directly compared with the findings with those from the CHARTER study.

In conclusion, the MNC method can control FDR at a predetermined level. No relationship between serostatus and cognitive impairment was found through this study.

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Conflicts of interest

There are no conflicts of interest.

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