## Title

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# Cross-Sectional Analysis of Cognitive Function in the MACS with Multivariate Normative Comparisons

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## Abstract

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

**Methods—**This project used data collected before October 2014 from bisexual/gay men from the Multicenter AIDS Cohort Study. 2,904 men (mean age 39.7yr, 52.7% seropositive) had complete

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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 (FDR). By contrast, the Frascati and the Gisslén criteria identified 24.54% and 11.36% of seronegative men as impaired. For seropositive men, the percent 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 infected men as having cognitive impairment. For each method, HIV-infection was not associated with cognitive impairment.

**Conclusions—**The MNC controls the FDR 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 includes women.

### Keywords

cognitive impairment; FDR; psychosocial tests; the Frascati criteria; the Gisslén criteria; HIV-associated neurocognitive disorders

## 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 (cART) 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 cut-off for impairment in individual cognitive domains, fails to account for correlations among different cognitive domain scores, which also affect the FDR. In order 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.

This method has been applied to individuals with HIV Disease drawn from the AGE$_{H}$IV Cohort Study,[11] where the rates of cognitive impairment based on the two standard criteria were compared to 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 (POPPY) 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 intercòrrelation 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 subjects 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 = 6,972) 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 1984/85, 688 enrolled in 1987/95, and 1350 men enrolled in 2001/03. Enrollment criteria includes: a) at least 18 years old; b) sexual relationship with at least 5 partners in the past five years; c) seronegative, or seropositive without clinical AIDS before highly active antiretroviral therapy (HAART), or seropositive with CD4 cell count and viral load known within six months before HAART initiation. The data used for this analysis were gathered on or before September 30, 2014.

Each individual enrolled in the MACS completed neuropsychological testing; initially, this was semi-annual. 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 semi-annually. 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 (CNS) 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 ten 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 (NP) 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 (see Supplemental Table 1). 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 standard deviation 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

In order to be classified as having neuropsychological impairment using the Frascati criteria, an individual participant must have two or more *domain* scores one standard deviation (SD) below the mean. In order 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 subjects across all domains. The method then compares the distance using the threshold that is determined by a pre-specified 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 inter-correlations among the various domain scores. The threshold is specifically chosen *a priori* and any distance beyond this threshold is deemed abnormal. In order 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 subjects 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 subjects 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 subjects who were treated as "healthy controls." To identify cognitive impairment within reference group, we implemented a "jackknife" technique where all the 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 subjects 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 subjects 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 subjects flagged as the same cognitive statuses by two criteria. Confidence intervals 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% confidence interval was obtained based on the 2.5$^{th}$ and 97.5$^{th}$ 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 subjects to those of the participants with 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 subjects included in study and subjects 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 R 3.4.1.

## Results

First, we observed that 28 subjects had T-scores below 10 for the motor speed/coordination domain, and their scores were truncated at 10, and 1 subject 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-Caucasian, 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 to 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 subjects (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 subjects 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 confidence intervals around these rates, and the rates of agreement between the various criteria are shown in Table 2 and Figure 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 to the seronegative group. Among seropositive subjects, no significant difference was found between those with and without comorbidities (*p* value=0.35).

Supplemental Table 2 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 be non-Caucasian, and they had consistently lower scores in all six NP 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 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 Caucasian and less fatigue, and were older.

In Table 3 we compare the characteristics of all the 2,904 men in the study as a function of their cognitive 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 Caucasian, 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 NP 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 Caucasians, more symptoms of depression, lower cognitive scores across all six domains and were less educated and older. Among the seropositive subjects, there was no significant difference in cognitive impairment rates as a function of viral suppression (cognitively impaired 22.90%, n=345, among virally suppressed subjects; 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=1,454, 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 inter-correlations 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 present 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 subjects.

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 NP 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 paper, 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 six 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. Unfortunately, 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 health care 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 subjects who had comorbidities may have a higher impairment rate than those subjects who did not have any comorbidities, if we had the information on every subject. 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 to the findings with those from the CHARTER study.

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

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Z.W. contributed to data analysis, interpretation and writing of the manuscript, and was responsible for producing and submitting the final manuscript.

S.A.M. contributed to data interpretation, data sharing and writing of the manuscript.

Y.C. supervised data analysis and interpretation and contributed to writing of the manuscript.

L.K. contributed to data interpretation, data collection and writing of the manuscript.

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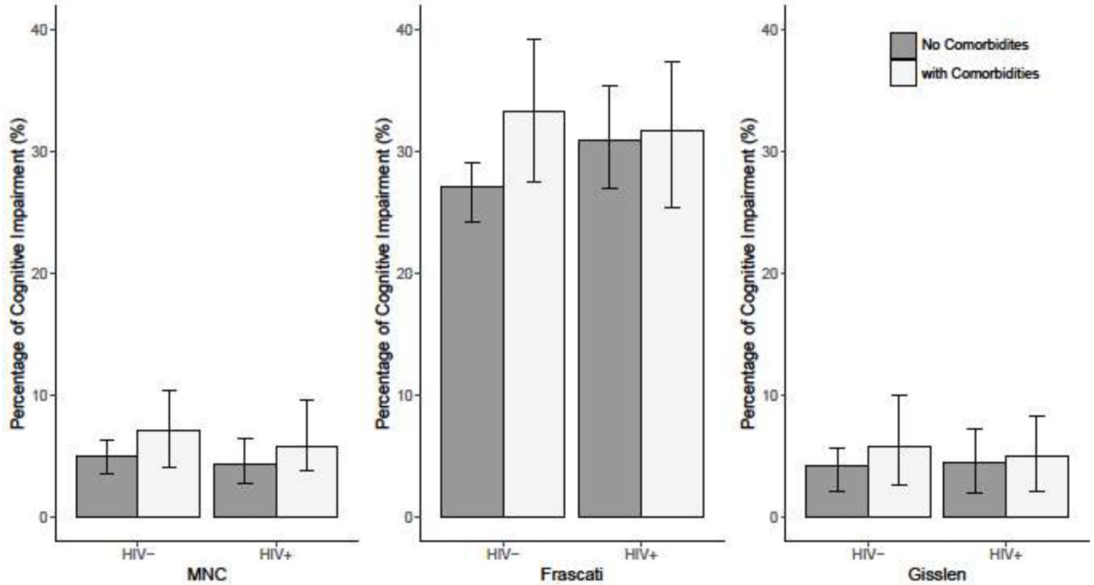


**Figure 1:**
Cognitive impairment classification results (seronegative without comorbidities as healthy control reference group)

## Table 1:

Comparison between seropositive and seronegative subjects

| | All (2,904) | HIV− (1,373) | HIV+ (1,531) | *p* value | Cohen's d/h |
|---|---|---|---|---|---|
| **Age** | 39.70±9.83 (2,904) | 40.99±11.10 (1,373) | 38.55±8.38 (1,531) | <.001 | .25 |
| **Non-Caucasian** | 30.82% (2,904) | 26.22% (1,373) | 34.94% (1,531) | <.001 | .092 |
| **>12 yrs education** | 80.72% (2,904) | 84.56% (1,373) | 77.27% (1,531) | <.001 | .12 |
| **High blood pressure** | 33.52% (2,094) | 38.77% (957) | 29.11% (1,137) | <.001 | .10 |
| **Diabetes** | 19.49% (1,180) | 20.38% (579) | 18.64% (601) | .49 | .018 |
| **Dyslipidemia** | 73.52% (1,216) | 71.60% (588) | 75.32% (628) | .16 | .055 |
| **Current alcohol use** | 38.85% (2,904) | 41.10% (1,373) | 36.82% (1,531) | .021 | .046 |
| **Current illicit drug use**[1] | 48.50% (2,876) | 44.49% (1,360) | 52.11% (1,516) | <.001 | .087 |
| **Drug with needle** | 4.75% (2,866) | 3.61% (1,356) | 5.76% (1,510) | .009 | .022 |
| **# of CD4 positive cells** | 725.07±381.43 (2,839) | 970.46±333.65 (1,338) | 506.33±272.84 (1,501) | <.001 | 1.53 |
| **Depression (CESD)** | 11.40±10.60 (2,818) | 10.44±10.15 (1,336) | 12.27±10.92 (1,482) | <.001 | .17 |
| **Cognitive domains** | | | | | |
| **Motor** | 46.89±10.53 (2,904) | 46.97±10.57 (1,373) | 46.82±10.50 (1,531) | .70 | .014 |
| **Executive** | 49.95±9.44 (2,904) | 50.16±9.31 (1,373) | 49.76±9.55 (1,531) | .26 | .042 |
| **Speed** | 49.71±8.77 (2,904) | 50.22±8.83 (1,373) | 49.25±8.69 (1,531) | .003 | .11 |
| **Learn** | 49.69±9.33 (2,904) | 49.83±9.20 (1,373) | 49.57±9.45 (1,531) | .46 | .028 |
| **Memory** | 49.88±9.48 (2,904) | 49.93±9.33 (1,373) | 49.84±9.61 (1,531) | .79 | .010 |
| **Working Memory** | 49.24±9.18 (2,904) | 49.43±9.37 (1,373) | 49.08±9.02 (1,531) | .31 | .038 |
| **Fatigue often**[2] | 25.11% (1,346) | 20.57% (632) | 29.13% (714) | <.001 | .088 |
| **Poor social functioning**[3] | 11.14% (1,346) | 8.07% (632) | 13.87% (714) | .001 | .058 |
| **Poor general health**[4] | 19.38% (1,347) | 12.50% (632) | 25.45% (715) | <.001 | .13 |
| **Individual gross income ≥ 50,000** | 24.75% (1,826) | 30.56% (818) | 20.04% (1,008) | <.001 | .11 |
| **Emotionally unstable**[5] | 16.42% (1,346) | 14.40% (632) | 18.21% (714) | .070 | .039 |
| **Current smoking** | 38.14% (2,863) | 34.08% (1,347) | 41.75% (1,516) | <.001 | .083 |
| **Insomnia** | 30.71% (1,501) | 24.09% (739) | 37.14% (762) | <.001 | .14 |

Percentage (%) is shown for categorical variable. Mean ± SD is computed for continuous variable. Number of subjects having such a variable with non-missing data is displayed in parenthesis.

[1] including marijuana, cocaine, heroin and uppers

[2] 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 <50

[3] 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<50

[4] 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 <50

[5] 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<50

**Table 2:**

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

| | | Seronegative (n=1,373) | | | Seropositive (n=1,531) | | |
|---|---|---|---|---|---|---|---|
| | | **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 subjects 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%)

## Table 3:

Comparison between cognitively impaired and not impaired subjects by MNC (seronegative without comorbidities as healthy control reference)

| | Impaired (n=540) | Not Impaired (n=2,364) | *p* Value | Cohen's d/h |
|---|---|---|---|---|
| **Age** | 41.65±10.47 (540) | 39.26±9.63 (2,364) | <.001 | .24 |
| **Non-Caucasian** | 39.44% (540) | 28.85% (2,364) | <.001 | .11 |
| **>12 yrs education** | 73.52% (540) | 82.36% (2,364) | <.001 | .14 |
| **High blood pressure** | 35.08% (400) | 33.13% (1,675) | .49 | .021 |
| **Diabetes** | 16.02% (256) | 20.45% (924) | .13 | .045 |
| **Dyslipidemia** | 72.01% (268) | 73.95% (948) | .58 | .028 |
| **Current alcohol use** | 30.45% (532) | 40.75% (2,364) | <.001 | .11 |
| **Current illicit drug use**[1] | 44.76% (534) | 49.36% (2,342) | .061 | .052 |
| **Drug with needle** | 6.78% (531) | 4.28% (2,335) | .020 | .025 |
| **# of CD4 positive cells** | 702.20±367.71 (524) | 730.24±384.35 (2,315) | .12 | .074 |
| **Depression (CESD)** | 12.79±11.38 (524) | 11.08±10.39 (2,294) | .002 | .16 |
| **Cognitive domains** | | | | |
| **Motor** | 38.43±15.01 (540) | 48.82±8.06 (2,364) | <.001 | 1.07 |
| **Executive** | 41.79±11.32 (540) | 51.82±7.84 (2,364) | <.001 | 1.17 |
| **Speed** | 42.46±8.97 (540) | 51.37±7.83 (2,364) | <.001 | 1.10 |
| **Learn** | 41.40±10.14 (540) | 51.59±8.01 (2,364) | <.001 | 1.21 |
| **Memory** | 41.55±10.00 (540) | 51.79±8.25 (2,364) | <.001 | 1.19 |
| **Working Memory** | 45.28±10.42 (540) | 50.15±8.63 (2,364) | <.001 | .54 |
| **Fatigue often**[2] | 26.48% (287) | 24.74% (1,059) | .60 | .018 |
| **Poor social functioning**[3] | 14.98% (287) | 10.10% (1,059) | .026 | .049 |
| **Poor general health**[4] | 22.53% (288) | 18.79% (1,059) | .34 | .028 |
| **Individual gross income ≥ 50,000** | 19.73% (370) | 26.03% (1,456) | .015 | .065 |
| **Emotionally unstable**[5] | 17.42% (287) | 16.15% (1,059) | .67 | .013 |
| **Current smoking** | 40.56% (535) | 37.59% (2,328) | .22 | .032 |
| **Insomnia** | 31.61% (329) | 30.46% (1,172) | .74 | .012 |

Percentage (%) is shown for categorical variable. Mean ± SD is computed for continuous variable. Number of subjects having such a variable with non-missing data is displayed in parenthesis.

[1] including marijuana, cocaine, heroin and uppers

[2] 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 <50

[3] 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<50

[4] 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 <50

[5] 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<50

## Table 4:

Comparison between cognitively impaired and not impaired among seropositive subjects by MNC (seronegative without comorbidities as healthy control)

| | Impaired (n=288) | Not Impaired (n=1,243) | *p* Value | Cohen's d/h |
|---|---|---|---|---|
| **Age** | 40.26±9.36 (288) | 38.16±8.09 (1,243) | <.001 | .25 |
| **Non-Caucasian** | 45.14% (288) | 32.58% (1,243) | <.001 | .14 |
| **>12 yrs education** | 69.79% (288) | 79.00% (1,243) | .001 | .14 |
| **High blood pressure** | 30.57% (229) | 28.74% (908) | .64 | .019 |
| **Diabetes** | 14.07% (135) | 19.96% (466) | .16 | .060 |
| **Dyslipidemia** | 73.45% (147) | 75.88% (481) | .63 | .036 |
| **Current alcohol use** | 26.50% (283) | 39.19% (1,235) | <.001 | .13 |
| **Current illicit drug use**[1] | 49.82% (285) | 52.64% (1,231) | .43 | .033 |
| **Drug with needle** | 7.45% (282) | 5.37% (1,228) | .23 | .021 |
| **# of CD4 positive cells** | 503.83±284.30 (280) | 506.90±270.26 (1,221) | .87 | .011 |
| **Depression (CESD)** | 14.36±11.90 (279) | 11.78±10.63 (1,203) | <.001 | .24 |
| **Cognitive domains** | | | | |
| **Motor** | 37.98±14.63 (288) | 48.87±8.00 (1,243) | <.001 | 1.13 |
| **Executive** | 41.47±11.80 (288) | 51.68±7.78 (1,243) | <.001 | 1.18 |
| **Speed** | 42.22±9.05 (288) | 50.88±7.74 (1,243) | <.001 | 1.08 |
| **Learn** | 41.15±9.87 (288) | 51.52±8.19 (1,243) | <.001 | 1.21 |
| **Memory** | 41.32±10.19 (288) | 51.81±8.31 (1,243) | <.001 | 1.21 |
| **Working Memory** | 45.10±9.89 (288) | 50.00±8.54 (1,243) | <.001 | .56 |
| **Fatigue often**[2] | 30.19% (159) | 28.83% (555) | .82 | .014 |
| **Poor social functioning**[3] | 18.87% (159) | 12.43% (555) | .052 | .065 |
| **Poor general health**[4] | 28.13% (160) | 24.68% (555) | .44 | .026 |
| **Individual gross income ≥ 50,000** | 19.12% (204) | 20.27% (804) | .79 | .012 |
| **Emotionally unstable**[5] | 22.01% (159) | 17.12% (555) | .20 | .050 |
| **Current smoking** | 41.12% (287) | 41.90% (1,229) | .86 | .009 |
| **Insomnia** | 38.95% (172) | 36.61% (590) | .64 | .025 |

Percentage (%) is shown for categorical variable. Mean ± SD is computed for continuous variable. Number of subjects having such a variable with non-missing data is displayed in parenthesis.

[1] including marijuana, cocaine, heroin and uppers

[2] 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 <50

[3] 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<50

[4] 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 <50

[5]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<50