# HIGH FREQUENCY OF NEUROCOGNITIVE DISORDERS IN OLDER HIV-INFECTED PATIENTS DESPITE A SUSTAINED VIROLOGICAL AND IMMUNOLOGICAL RESPONSE ON CART: THE SIGMA STUDY

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**# 459**

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## ABSTRACT*

**Background:** During aging, HIV infection could accelerate the emergence of cognitive disorders, despite the widespread use of virologically effective combination ART (cART).

**Methods:** We report here the neurocognitive subset (Neurosigma) of the Sigma study, an observational, cross-sectional study designed to describe the medical conditions and the psychosocial status of patients aged 60 years and more in the Bicetre HIV Cohort, an hospital cohort of 1350 HIV-infected patients. Demographic data, medical and therapeutic history, cardiovascular risk factors (CRF), plasma HIV RNA levels, and CD4 counts since HIV diagnosis were collected. Subjects with active neurologic or psychiatric diseases and low educational level were excluded. Subjects underwent a brief neuropsychological exam using the Trailmaking A/B and the Digit Symbol yielding a composite NPZ3 score (assessing psychomotor speed, attention, cognitive sequencing, and shifting cognitive sets). The Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS), and the Instrumental Activity of Daily Living (IADL) were performed.

**Results:** Among the 75 patients older than 60 years, 37 (49%) achieved the Neurosigma substudy. At enrolment, all patients except 1 were treated with cART; 73% were men. Median age was 67 years (range 60 to 84). Median duration of HIV infection and of ART were respectively 11 (IQR 5 to 17) and 10 (IQR 3 to 14) years. Median nadir CD4 count was 207 cells/µL (IQR 92 to 293), whereas the last median CD4 count was 519 cells/µL (IQR 439 to 675). HIV RNA was <40 copies/mL in all treated patients. One or more CVR factors was present in 25 patients (diabetes 22%, hypertension 49%, dyslipidemia 30%, tobacco use 22%). A neurocognitive impairment was detected in 18 patients (49%). MMSE was abnormal (<-1.65 SD) in 6 (16%) patients. Severe impairment (<-2) of NPZ3 was observed in 11 patients (30%) including 4 with abnormal IADL and mild (-2≤NPZ3<-1) in 8 (21%). GDS was abnormal (>5) in 7 patients (19%).

**Conclusions:** Despite a sustained response to cART, neurocognitive disorders are more frequent in old HIV+ patients than in the general aging population, but are underdiagnosed by their physicians. In our patients, subcortical types of cognitive impairment remain more predominant than neocortical types. The respective role of HIV, ART, and co-morbidities is debated. Longitudinal studies are needed to assess the outcome of these disorders in aging and to determine their predictive factors.

* Updated on 31 January 2009.

## BACKGROUND

Longer life expectancy of people living with HIV treated with long term-sustained combination antiretroviral therapy (cART) focuses on the impact of a chronic HIV infection on the process of normal aging.

During aging, HIV infection could accelerate the emergence of cognitive disorders despite the widespread use of virologically effective cART.

We report here the neurocognitive subset (Neurosigma) of the Sigma study. The cross-sectional Sigma study was designed to describe the medical conditions and the psychosocial status of patients aged 60 years and more in the Bicetre HIV Cohort, an hospital cohort of 1350 HIV-infected patients.

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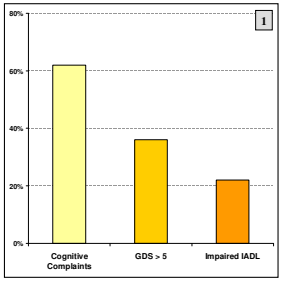
## RESULTS

| Table 1. Demographic and disease features at entry [median (IQR)], [N (%)] | | N = 37* |
|---|---|---|
| Gender and exposure group | MSM | 17 (46%) |
| | Non-MSM men | 10 (27%) |
| | Women | 10 (27%) |
| Age at study entry *(years)* | | 67 (64 - 74) |
| Educational level *(years)*** | | 11 (10 - 15) |
| Time from HIV diagnosis *(years)* | | 10,8 (5.3 - 16.7) |
| Time from first ART onset *(years)* | | 10,2 (4.2 - 13.4) |
| CDC stage C | | 8 (22%) |
| Nadir CD4+ T cell *(cells/µL)* | | 207 (92 – 293) |
| Last CD4+ T cell *(cells/µL)* | | 519 (439 – 675) |
| On cART<br>% HIV load < 40 copies/mL on cART | | 36/37<br>100% |
| Duration with HIV load < 40 copies/mL *(years)* | | 3.7 (1.9 – 5.6) |
| Cardiovascular Risk (N patients) | | 25 (68%) |

* Among the 75 patients older than 60 years in the Bicetre HIV Cohort, 5 declined enrollment, 13 were excluded (including 8 not fluent in French) and 20 were unavailable between April and August 2008.
**At least, 37 (49%) achieved the Neurosigma substudy.**
** 15 patients (41%) obtained high school diploma or higher.



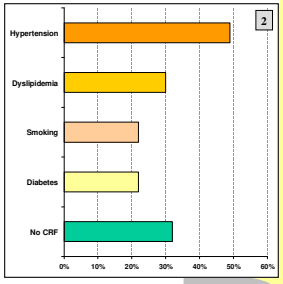
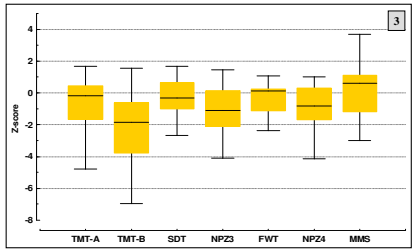




**Figure 1. Self-reported cognitive complaints, mood symptoms, impairment in instrumental activities of daily-living.**

**Figure 2. Proportion of patients with cardio-vascular risk factors (CRF).**

**Figure 3. Neuropsychological assessment of participants expressed as Z-scores: NPZ3** (TMT-A, TMT-B, Digit Symbol Test); **NPZ4** (TMT-A, TMT-B, Digit Symbol Test + Five-Word Test); **Mini-Mental Test.**

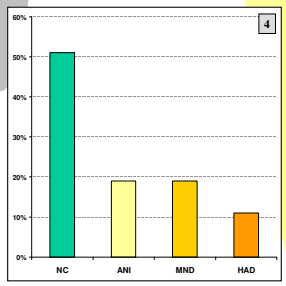
**Figure 4. Proportion of patients with neurocognitive impairment according to HAND criteria** (NC = normal cognition, ANI = asymptomatic neurocognitive impairment; MND = mild neurocognitive disorder; HAD = HIV-associated dementia).




| Table 2. Neurocognitive impairment and Cardiovascular Risk | NCI | NC |
|---|---|---|
| CRF | 13 | 12 |
| No CRF | 5 | 7 |

**Chi-square test: p = 0.556**
NCI = neurocognitive impairment, NC = normal cognition, CRF = cardiovascular risk factors

**Cognitive Pattern**
**Subcortical = 9 (50%)**
**Neocortical = 3 (17%)**
**Mixed = 6 (33%)**

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## CONCLUSIONS

- **Despite a sustained response to cART, neurocognitive impairment (NCI) can be detected in 49% of HIV+ patients aged of 60 years and more, using a brief neuropsychological battery.**
- **In our 37 patients, cardio-vascular risk factors are highly prevalent (68%), but are not associated with NCI.**
- **Subcortical type of NCI is more predominant than neocortical type.**
- **The respective roles of HIV, cART, and co-morbidities remain debated. Further studies (including brain MRI and CSF HIV load) are ongoing to determine factors associated with NCI in aging.**

## METHODS

**Participants:** The Neurosigma study included 37 of the 75 HIV-infected patients aged of 60 years and more at 31 December 2008 in the Bicetre HIV Cohort. Exclusion criteria were (i) active neurological or major psychiatric (mental retardation, psychotic disorders, current substance abuse) or severe medical diseases likely to interfere with subjects' ability to complete the study; (ii) very low educational level or lack of fluency in French. Informed consent from subjects was obtained prior to enrollment.

**Data collection:** Demographic data, medical and therapeutic history, cardiovascular risk factors (CRF), plasma HIV RNA levels, and CD4 T cell (nadir and last count) were collected.

**Neuropsychological evaluation:** All participants completed a brief battery of neuropsychological tests. We used the Brief NeuroCognitive Screen (*Ellis, 2005*) including the Trail Making Test (TMT) A and B and the WAIS-R Digit Symbol Task (DST), to assess psychomotor speed, attention/working memory and mental flexibility. The Five Word Test (FWT), a serial verbal memory test with semantic cuing, was used for investigating verbal episodic memory (*Dubois, 2002*). Moreover, the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS), the PROQOL-HIV and the EuroQol (EQ-5D) and the Instrumental Activity of Daily Living (IADL) were performed.

**Data analysis:** Items of PROQOL-HIV (# 29, 30 & 31) and of EuroQol (Self-Care and Usual Activities) were used to assess self-reported cognitive complaints.

A z-score for each test was calculated by subtracting a normative mean from each subject's score and then dividing by the appropriate standard deviation for each test. For FWT, the results were processed first by a Total Weighted Score which give a higher coefficient for free recalls than cued recalls (*Croisile, 2007*). Published norms adjusted for age, gender and education were utilized. NPZ3 was calculated as the mean of the z-scores on the 3 BNCS tests and NPZ4 as the mean of the z-scores on the 3 BNCS tests and FWT. At last, diagnosis of neurocognitive impairment was established, using the HIV-Associated Neurocognitive Disorders (HAND) criteria (*Antinori, 2007*).