Good Neurocognitive Performance Measured by the International HIV Dementia Scale in Early HIV-1 Infection

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Objective: To evaluate neurocognitive performance in patients with preserved immunological status using the International HIV Dementia Scale (IHDS) and compare patients on and off highly active antiretroviral therapy (HAART).

Design: Cross-sectional study.

Methods: Outpatients with more than 350 CD4 cells per cubic millimeter underwent evaluation by means of the IHDS, a cross-cultural scale designed to identify HIV-positive patients at risk for dementia.

Results: A total of 260 patients were included, 158 on HAART and viral load <1000 copies per mL and 102 on treatment naive. Mean age was 38.2 (SD 8.03) years, 86% were male. Mean score was 10.9 (SD 1.77). Only age correlated with a significantly different score; younger patients performed better. When patients on and off HAART were compared, we found no significant differences in age, sex, time from diagnosis, educational level, risk factor for HIV acquisition, and current CD4 count. CD4 nadir was lower for patients younger than 50 and more than 80% in those older than 50.2,5 There was no difference according to efavirenz use.

Conclusions: Patients with preserved immunity performed well on IHDS. It didn’t seem to be any difference between patients on and off HAART regarding neurocognitive status.

Key Words: HIV infection, HIV dementia, international HIV dementia scale, neurocognitive disorders

(J Acquir Immune Defic Syndr 2009;52:522–526)

INTRODUCTION

Cognitive and motor impairment is still recognized as a common complication in HIV-1 infection, presenting as a wide spectrum of disorders ranging from HIV-associated asymptomatic neurocognitive impairment (ANI) to severe forms of cognitive impairment, known as HIV-1–associated dementia (HAD).

In early HIV-1 infection, prevalence of ANI is about 20%.1 In patients with AIDS, prevalence of any cognitive impairment is 52% in those younger than 50 and more than 80% in those older than 50.2,5

The role of HIV-1 proliferation on the development of HIV dementia is controversial. Although viral strains replicating in brain macrophages may play a role in the pathogenesis of brain injury, a heavy viral burden in brain has not been linked consistently with clinical HIV dementia.2,3

Neurocognitive impairment should be diagnosed and assessed early in the course of HIV-1 infection because it is associated with increased mortality,4,5 may interfere with adherence,6 and may be treated with antiretroviral agents. Giancola et al7 demonstrated that control of plasma levels of HIV-1 RNA in less advanced HIV patients affected by mild neurocognitive disorders could be sufficient to improve the deficits. As HIV is now a chronic and manageable disease, the relative importance of neurological morbidity has increased. Neuropsychological testing is a critical component of the diagnosis, but it is time consuming, language and educational dependent, and often not available in developing countries.

Mini Mental State Exam by Folstein et al8 was designed to screen for cortical dementia, it is therefore not sensitive for detecting subcortical dementia such as HIV dementia.9 The HIV Dementia Scale was designed as a brief but sensitive screening instrument to identify HIV-1 infected patients at risk for dementia. However, it is difficult for nonneurologists to administer and includes subtests which may be difficult for individuals with a nonwestern educational background.

Sacktor et al10,11 developed a practical cross-cultural screening instrument, the International HIV Dementia Scale (IHDS). It offers several advantages: it is easy to perform, requires only 2–3 minutes by nonneurologists in an outpatient setting, requires no special instrumentation, and detects subcortical damage such as HIV dementia. It does not require knowledge of the English language.

The sensitivity and specificity of the IHDS are comparable to the sensitivity (71%) and specificity (46%) of the Grooved Pegboard nondominant hand test, an established test for HIV dementia.12-14 The IHDS identifies individuals at risk for HIV dementia within the International community, particularly in developing countries. However, it should not be used as a replacement for a full neuropsychological testing to confirm a diagnosis of HIV dementia.
According to the Department of Health and Human Services (DHHS) guidelines, most asymptomatic HIV-1–infected patients with CD4 cell count \( >350 \) cells per cubic millimeter would not require antiretroviral therapy.\(^\text{15}\) Nevertheless, there is concern that patients who do not receive antiretroviral therapy may develop neurocognitive impairment despite preserved immunological status. The impact of continuing viral replication in this population is not known. The mean CD4 cell count for new cases of HIV dementia is increasing.\(^\text{16}\)

Sacktor et al\(^\text{17}\) assessed the temporal trends in the incidence rates of HIV dementia from 1990 to 1998 in the Multicenter AIDS Cohort Study. They found that the incidence decreased dramatically since the introduction of highly active antiretroviral therapy (HAART) in 1996 compared with the incidence rates from 1990 to 1992. However, they also found that the proportion of new cases of HIV-1–associated dementia with higher CD4 count increased compared with the early 1990s.

Our hypothesis was that asymptomatic HIV-infected patients with high CD4 cell count could be at risk of developing neurocognitive impairment, particularly for those who do not receive HAART.

The objective of this study was to evaluate the presence of neurocognitive impairment in patients with preserved immunological status using the new IHDS in a developing country and to compare patients with controlled plasma viral load replication on HAART with those not receiving HAART.

METHODS

This was a cross-sectional study. The population consisted of outpatients with CD4 cell count higher than \( 350 \) cells per cubic millimeter from 2 HIV clinics and 1 hospital in Buenos Aires. The Ethics committee of the participating institutions approved the study, and participants signed informed consent to participate. Patients were eligible if they had confirmed HIV-1 infection, were older than 18 years, had a CD4 cell count above \( 350 \) cells per cubic millimeter, and HIV-1 viral load measured in the previous 3 months. Patients with a history of psychiatric disease, including depression, current use of recreational drugs, and current or previous opportunistic infections, and patients on HAART with viral load \( >3 \) log were excluded. All patients accomplishing inclusion criteria, who assisted to an outpatient visit, were offered to participate in the study.

Patients were divided in 2 groups: those on HAART and VL \( <1000 \) and those treatment-naïve. All the patients underwent evaluation by means of IHDS, which consist of 3 subsets: timed fingertapping, timed alternating hand sequence test, and recall of 4 words at 2 minutes (score \( \geq 10 \) suggestive of dementia). Four different physicians, all specialists in infectious diseases, performed the test.

The following variables were assessed: age, gender, educational level, risk factor for acquisition of HIV infection, time from diagnosis of HIV infection, current CD4 cell count, CD4 cell count nadir, and current viral load. Participants on HAART were stratified according to the use of efavirenz.

We analyzed the scores according to different variables and then compared those patients on HAART with those not receiving HAART.

RESULTS

During a 2-month period, 260 subjects were enrolled, 158 on HAART, and 102 treatment naive. Mean age was 38.2 years, (SD 8.03, \( r = 21–73 \)), 86% were men, 96% acquired HIV sexually (64% men who have sex with men, 32% heterosexual) (Table 1).

Mean score was 10.9 (SD 1.77). Of all the variables analyzed, only age was found to be associated with a different performance. The score was significantly higher in the group of patients 21–44 years old compared with those 45–73 years old. Mean scores were 11.1 and 10.2, respectively; \( P < 0.001 \), Fisher (Table 2).

None of the other variables showed a statistically significant difference. Regarding educational level, most patients were highly educated, so it was not possible to perform the analysis. More than 90% of participants had finished high school or had a university degree.

Eighty-three patients were on efavirenz, they did not perform different from the rest of the population (Table 1). Age, gender, risk factor for HIV acquisition, time from diagnosis of HIV infection, educational level, and current CD4 cell count were similar between groups. CD4 cell count nadir was lower for patients on HAART: 246.0 (200.95) and 492.7 (233.33) for patients off HAART, \( P < 0.001 \) (t test).

Median current viral load was \( <50 \) copies per milliliter (interquartile range: \( <50 \) to \( <50 \)) and 21,102 copies per milliliter (interquartile range: 6360–83,900), respectively.

When we compared both groups, those on therapy with those off, we found no difference between the distribution of...
scores: mean, 11.0 (2.08) and mean, 10.08 (1.17), respectively, 
\[ P = 0.70 \text{(Fisher)}. \]

Finally, the score was classified as ≤10 points or >10 points. A logistic regression model analysis was performed to assess if any of the variables analyzed was an independent risk factor for a lower score. The score was considered the dependent variable. According to the logistic regression model, only age was related to the score. Advanced age was a significant risk factor for IHDS score ≤10 (odds ratio = 3.5, 95% confidence interval: 1.36 to 8.99; \[ P < 0.01 \]). Younger participants, those aged 21–44, performed better (Fig. 1).

**DISCUSSION**

The results of our study do not confirm our hypothesis. According to the IHDS, our population do not have a significant risk of HIV-associated dementia. Besides, the presence of controlled plasma viral load replication does not seem to show any benefit on the risk of developing HIV dementia in this population.

In univariate and multivariate analysis, only older patients were at higher risk. Neither gender, risk factor, time from diagnosis of HIV-1 infection, current CD4 cell count and viral load, nor CD4 cell count nadir were associated with risk. It is well known that efavirenz may cause neurological side effects and could interfere in neurocognitive performance. We did not find any difference in patients receiving efavirenz and those not.

Epidemiological research initiatives identified an increased rate of HIV-associated dementia among older patients. It is not clear if there is an additive or synergistic relationship between aging and HIV on neuropsychological

**TABLE 1. Variables Analyzed in Patients on and Off HAART**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 260)</th>
<th>On HAART (n = 158)</th>
<th>Off HAART (n = 102)</th>
<th>[ P ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (n = 259), n (%)</td>
<td>222/259 (86)</td>
<td>131/158 (83)</td>
<td>91/102 (89)</td>
<td>0.21 (Fisher)</td>
</tr>
<tr>
<td>Mean age (n = 259)</td>
<td>38.2 (8.03)</td>
<td>38.9 (7.78) (n = 157)</td>
<td>37.1 (8.31) (n = 102)</td>
<td>0.07 (t test)</td>
</tr>
<tr>
<td>Risk factor for HIV acquisition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVDU, n (%)</td>
<td>9/241 (4)</td>
<td>6/141 (4)</td>
<td>3/100 (3)</td>
<td>0.09 (χ², Pearson)</td>
</tr>
<tr>
<td>Heterosexual, n (%)</td>
<td>78/241 (32)</td>
<td>53/141 (38)</td>
<td>25/100 (25)</td>
<td></td>
</tr>
<tr>
<td>MSM, n (%)</td>
<td>154/241 (64)</td>
<td>82/141 (58)</td>
<td>72/100 (72)</td>
<td></td>
</tr>
<tr>
<td>Current CD4 (n = 260)</td>
<td>620.2 (239.76)</td>
<td>632.1 (239.98) (n = 158)</td>
<td>601.8 (239.43) (n = 102)</td>
<td>0.32 (t test)</td>
</tr>
<tr>
<td>Current viral load (n = 255), median (interquartile range)</td>
<td>50 (50–10,850)</td>
<td>50 (50–50) (n = 157)</td>
<td>21,102 (6630–83,900) (n = 98)</td>
<td>&lt;0.001 (Wilcoxon, w = 12,686)</td>
</tr>
<tr>
<td>CD4 cell count nadir (n = 250)</td>
<td>345.7 (246.13)</td>
<td>246.0 (200.95) (n = 149)</td>
<td>492.7 (233.33) (n = 101)</td>
<td>&lt;0.001 (t test)</td>
</tr>
<tr>
<td>Efavirenz use (n = 155), n (%)</td>
<td>—</td>
<td>83/155 (54)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Educational level (n = 225)</td>
<td>209/225 (93)</td>
<td>118/128 (92)</td>
<td>91/97 (94)</td>
<td>0.80 (Fisher)</td>
</tr>
<tr>
<td>Maximal viral load, mean (SD) (n = 233)</td>
<td>288,995.2 (843,002.00)</td>
<td>270,953.7 (319,552.31)</td>
<td>314,290.6 (1,254,076.90)</td>
<td>&lt;0.001 (t test)</td>
</tr>
</tbody>
</table>

MSM, men who have sex with men.

**TABLE 2. Neurological Performance According to Different Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Strata</th>
<th>n</th>
<th>Mean Score</th>
<th>[ P ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (n = 259)</td>
<td>21–44</td>
<td>210</td>
<td>11.1 (1.85)</td>
<td>&lt;0.001 (Fisher)</td>
</tr>
<tr>
<td></td>
<td>45–73</td>
<td>49</td>
<td>10.2 (1.17)</td>
<td></td>
</tr>
<tr>
<td>Sex (n = 259)</td>
<td>Men</td>
<td>222</td>
<td>11.0 (1.86)</td>
<td>0.45 (Fisher)</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>37</td>
<td>10.6 (1.06)</td>
<td></td>
</tr>
<tr>
<td>Risk factor for acquisition of HIV-1 infection (n = 241)</td>
<td>Heterosexual</td>
<td>78</td>
<td>10.5 (1.16)</td>
<td>0.003 (χ², Pearson)</td>
</tr>
<tr>
<td></td>
<td>MSM</td>
<td>154</td>
<td>11.0 (1.06)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IVDU</td>
<td>9</td>
<td>10.1 (0.85)</td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis of HIV-1 infection (n = 251)</td>
<td>&lt;5 yrs</td>
<td>84</td>
<td>10.8 (1.14)</td>
<td>0.48 (Fisher)</td>
</tr>
<tr>
<td></td>
<td>≥5 yrs</td>
<td>167</td>
<td>11.0 (2.05)</td>
<td></td>
</tr>
<tr>
<td>Current CD4 cell count (n = 260)</td>
<td>≤500 mm³</td>
<td>96</td>
<td>11.1 (2.50)</td>
<td>0.41 (Fisher)</td>
</tr>
<tr>
<td></td>
<td>&gt;500 mm³</td>
<td>164</td>
<td>10.8 (1.15)</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count nadir (n = 250)</td>
<td>≤200 mm³</td>
<td>76</td>
<td>11.0 (2.36)</td>
<td>0.66 (Fisher)</td>
</tr>
<tr>
<td></td>
<td>&gt;200 mm³</td>
<td>174</td>
<td>10.8 (1.11)</td>
<td></td>
</tr>
<tr>
<td>Current viral load (n = 246)</td>
<td>≥1000 copies/mL</td>
<td>91</td>
<td>10.8 (1.18)</td>
<td>0.67 (Fisher)</td>
</tr>
<tr>
<td></td>
<td>&lt;1000 copies/mL</td>
<td>155</td>
<td>11.0 (2.04)</td>
<td></td>
</tr>
<tr>
<td>Efavirenz as part of HAART (n = 155)</td>
<td>Yes</td>
<td>83</td>
<td>11.1 (1.72)</td>
<td>0.13 (Fisher)</td>
</tr>
</tbody>
</table>

MSM, men who have sex with men; IVDU, intravenous drug users.
testing performance. The presence of coexisting diseases, particularly neurodegenerative disorders among older patients limits our ability to identify HIV-specific etiologies. HIV infection could increase the risk for other age-related neurodegenerative disorders. Historically, there was little need to consider age-related neurodegenerative diseases as a contributing factor to neurocognitive impairment in HIV infection because the young age of HIV-infected population. Today, prolonged life expectancy, arise the issue of aging as a relevant factor in neurocognitive impairment. HIV infection could lower the threshold for the clinical presentation of other neurodegenerative diseases.

Early diagnosis of HIV neurocognitive impairment is crucial, particularly, because it is a potentially treatable condition with antiretroviral therapy. The benefit of HAART on neuropsychological function in patients with advanced diseases is well known; neurocognitive improvement has been associated with a decline in cerebrospinal fluid HIV-1 RNA in patients who started HAART therapy after diagnosis of a cognitive deficit. IHDS proved to be an easy to perform tool in a Spanish-speaking population from a developing country. Besides, it proved not to be time consuming and could be provided by nonneurologists.

Within different regions, different subtypes (clades) of HIV-1 predominate, each with possible variations in disease progression and incidence of HAD. There has been some suggestions that the neurotoxicity of clade C is less than that of other clades. So far, most studies about incidence and prevalence of HAD have been conducted in the developed world and in North America, in particular, where clade B predominates. In Argentina, clades B and BF are the predominant clades.

Our study has several limitations. First, the population we studied has a preserved immune status and therefore the risk of HIV-associated dementia could be low. Second, IHDS has been developed to screen for HIV-associated dementia and probably is not sensitive enough to screen for HIV-1–associated minor cognitive disorders such as ANI or HIV-associated minor neurocognitive disorder. However, the most relevant limitation of IHDS has been shown to be specificity, not sensitivity. The IHDS cannot be used to distinguish between different stages of HIV dementia, although progressively lower mean IHDS scores did correspond to greater dementia severity in a previous study. Third, this was a cross-sectional analysis, and the sample size was not big enough to be powered to show differences according to some of the analyzed variables such as risk factor for HIV infection. Fourth, our population was mainly composed by men who have sex with men and highly educated patients; education is known to be a protecting factor for neurocognitive impairment. Finally, patients on HAART received drugs with different central nervous system penetration.

According to our results, patients with preserved immune status do not seem to be at high risk of developing clinically significant neurocognitive impairment measured by IHDS, and it does not seem to have any difference between those being on antiretroviral therapy with controlled plasma viral load and those who are not on antiretroviral therapy. Only older patients could be at higher risk.

ACKNOWLEDGMENT

The authors would like to thank Dr. Karl Goodkin for his substantial contribution to this paper.

REFERENCES


