Major Article

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# Prevalence of neurocognitive disorders and depression in a Brazilian HIV population

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**ABSTRACT**

**Introduction:** Combined antiretroviral therapy has enabled human immunodeficiency virus (HIV) carriers to live longer. This increased life expectancy is associated with the occurrence of degenerative diseases, including HIV-associated neurocognitive disorders (HAND), which are diagnosed via a complex neuropsychological assessment. The International HIV Dementia Scale (IHDS) is a screening instrument validated in Brazil for use in the absence of neuropsychological evaluation. HIV patients are frequently diagnosed with depression. We aimed to determine the prevalence of neurocognitive impairment using the IHDS and depressive disorders using the Hamilton Rating Scale for Depression (HAM-D17), compare the IHDS performance with the performances on the Timed Gait Test (TGT), the Digit Symbol Coding Test (DS) and the Brazilian version of the Scale of Instrumental Activities of Daily Living (IADL), and evaluate the association between the IHDS performance and clinical-demographic variables. **Methods:** One hundred fourteen patients were evaluated in a cross-sectional study conducted in a public outpatient clinic for infectious diseases in Marília City, State of São Paulo, Brazil. Data were collected following consultation. Statistical analysis was performed in accordance with the nature and distribution of the data and hypotheses. **Results:** According to the IHDS, 53.2% of the sampled patients were neuropsychologically impaired. According to the HAM-D17, 26.3% had depressive disorders. There were significant associations between the IHDS and the TGT and DS. Multiple regression analysis indicated that female gender, educational level, and cluster of differentiation 4 (CD4) levels were significantly and independently associated with neurocognitive impairment. **Conclusions:** The prevalence of neurocognitive impairment according to the IHDS is high and associated with female gender, education level, and low CD4 levels.

**Keywords:** HIV. Neurocognitive disorders. Depressive disorder.

## INTRODUCTION

Highly active antiretroviral therapy (HAART) has enabled the effective control of viral replication and immune status improvement in patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS), which has led to decreased mortality as a result of opportunistic infections[1] [2] [3]. This increased life expectancy is associated with an increased occurrence of degenerative diseases, including HIV-associated neurocognitive disorders (HAND)[2] [3]. The prevalence of cognitive impairment related to HIV remains high, despite the advent of HAART[3] [4] [5].

HIV-associated neurocognitive disorders are characterized by cognitive, motor, and behavioral alterations secondary to the preferential impairment of subcortical structures by the virus[6]. The current criteria for HAND are based on complex neuropsychological evaluations and the assessment of functional impact. Numerous instruments are utilized to identify neurocognitive impairment in HIV-infected patients in areas in which formal neuropsychological evaluation is not widely available[7].

The International HIV Dementia Scale (IHDS) is a recommended instrument that is particularly useful in outpatient evaluations[7] [8]. Recently validated in Brazil, the IHDS exhibited a sensitivity of 78.5% and a specificity of 80.8% for the identification of HIV-related dementia[9]. The prevalence of HAND in the validation study was estimated to be 52.4%. The international literature reports prevalence rates between 22.7 and 69% using current diagnostic criteria[10] [11] [12]. Limited Brazilian studies regarding the prevalence of HAND have been conducted[9] [13] [14].

Multiple factors are associated with neurocognitive disorders in HIV patients, with the most important factors as follows: age, duration of HIV infection, low CD4+ T lymphocyte counts (CD4), previous high plasmatic viral loads (VL), and psychiatric illness[10] [15] [16].

Other neuropsychological tests, such as the Timed Gait Test (TGT) and Digit Symbol Coding Test (DS), are used as complementary tools to identify neurocognitive impairment in HIV+ patients[17].

Individuals with HIV/AIDS are also frequently diagnosed with depression, with prevalence rates between 12 and 66%[18] [19].

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A previous study suggests an association between depression and neurocognitive disorders in HIV+ patients[20]. In Brazil, the prevalence of depression in HIV+ patients has been reported between 32 and 34.5%[13] [19].

Both neurocognitive disorders and depression can negatively impact quality of life, daily activities, and treatment adherence[21] [22] [23].

The objectives of this study were to determine the prevalence of neurocognitive impairment and depressive disorders in HIV+ patients, compare the performance of the IHDS with the performances of other neuropsychological assessment tools (TGT and DS) and a scale of instrumental activities of daily living, and evaluate the association between neurocognitive impairment and clinical-demographic variables.

## METHODS

A cross-sectional study was conducted in the affiliated clinic for Infectious Diseases of the *Faculdade de Medicina de Marília* (FAMEMA), Marília City, State of São Paulo, Brazil.

One hundred ninety-five patients with HIV/AIDS scheduled at the clinic in 2013 were recruited. The inclusion criteria were as follows: confirmed HIV infection and 18 years of age or older. The following conditions comprised exclusion criteria: incarcerated patients, active opportunistic infections, decompensated clinical illnesses, or hospitalization within the previous three months.

All patients were evaluated by the same researcher, who performed the interview and clinical evaluation. Laboratory data were collected from the patients' records. After consultation, the patients were invited to participate in the study. Following written informed consent, the following assessment methods were simultaneously administered.

### International HIV Dementia Scale

The IHDS comprises a method for screening neurocognitive disorders that evaluates memory/recall, motor speed and executive functions. Subjects with scores ≤10 were considered to exhibit neurocognitive impairment[7] [9].

### Hamilton Rating Scale for Depression

The Hamilton Rating Scale for Depression (HAM-D17) is an instrument based on the gradation of depressive symptoms that consists of a questionnaire conducted in accordance with an interview guide[24] [25]. Patients with scores >7 on the 17-item scale were considered to have a depressive disorder.

### Scale of Instrumental Activities of Daily Living

Developed from the Scale of Instrumental Activities of Daily Living (IADL) of Lawton and Brody and adapted to the Brazilian context[26] [27], this scale measures the degree of dependence/independence in performing the following tasks: using the telephone, traveling, shopping, preparing meals, performing housework, taking medications, and using money. Each item is assigned a score from 1-3, and higher scores indicate better performance. The patients were classified as totally dependent (7 points), partially dependent (8-20 points), or independent (21 points).

### Digit Symbol Coding Test

The DS is part of the Wechsler Adult Intelligence Scale and comprises a paper-pencil measure of processing speed in which subjects use a key of digits referenced by symbols and are required to fill in the correct symbol for each number as quickly as possible within a 120-second timeframe. The score represents the number of correct items completed. There is no cut-off value for normality; thus, the mean and standard deviation (SD) of the subjects' raw scores were calculated and subsequently used for comparison with the IHDS performance[28].

### Timed Gait Test

The TGT comprises a standardized procedure for the assessment of motor dysfunction in the lower extremities in patients with HIV-dementia; it consists of walking 10 yards and back as quickly as possible. The score represents the mean time of three trials, which is recorded in seconds and decimals. The mean and SD of the patients' scores were calculated for comparison with the IHDS performance[29].

### Central Nervous System Penetration-Effectiveness Rank

The Central Nervous System Penetration-Effectiveness Rank (CPE) comprises the score for the classification of the estimated penetration of antiretroviral drugs in the central nervous system (CNS). Higher scores are associated with better drug penetration in the CNS. The score was calculated for each participant who underwent HAART for >1 year[15].

### Statistical analysis

Descriptive analyses of the patients' demographic and clinical data were conducted by calculating the means and SDs for the continuous variables and the proportions for the categorical variables.

The patients with IHDS scores ≤10 were considered to exhibit neurocognitive impairment and were compared to the patients with scores >10 in relation to variables such as age, gender, educational level, time since HIV diagnosis, recent and lowest lifetime CD4 levels, recent and highest VL, and depression. We also performed a comparison of the TGT, DS, HAM-D17, and IADL scores between the patients with an IHDS score ≤10 or >10.

In the statistical analyses, Pearson's chi-squared tests, Student's t-tests, Fisher's exact tests, and Kruskal-Wallis tests were used in accordance with the nature and distribution of the data and the hypotheses. The Pearson correlation coefficient was used to evaluate the correlation between continuous variables.

Multiple regression analyses were conducted to measure the association between the IHDS performance and the following variables: gender, age, educational level, presence of co-morbidities, most recent and prior CD4 counts <200 cell/mm$^3$, most recent and prior VL >100,000 copies/ml, and depression. The Forward method was utilized with entry criteria of $p<0.05$ and removal criteria of $p<0.10$. A significance level of 0.05 was established. The Statistical Package for Social Science (SPSS)

software, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis.

### Ethical considerations

The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and approved by the *Comitê de Ética em Pesquisa Envolvendo Seres Humanos da Faculdade de Medicina de Marília* (protocol number 670/12).

## RESULTS

In 2013, 195 patients were scheduled at the outpatient clinic for infectious diseases; 13 patients were not included because they were transferred to other services (n=8) or died (n=5) prior to the initiation of data collection. Twenty-eight patients were incarcerated, and 15 patients met clinical criteria for exclusion, which indicated 139 patients were eligible to participate in the study. Twenty-two patients did not attend the scheduled appointment, and 3 patients refused to participate; thus, 114 patients were evaluated.

**Table 1** shows the clinical-demographic characteristics of the studied population. Of note, 50% (n=57) of the patients had other diseases. Metabolic or endocrine diseases were present in 26.4% (n=30) of the patients, and cardiovascular diseases were presents in 26.4% (n=30). The patients diagnosed with more than one associated disease accounted for 19.3% (n=22) of the subjects. Only 3.5% (n=4) of the patients were co-infected with hepatitis C virus.

Previous CNS infections occurred in 19.3% (n=22) of the patients, with neurotoxoplasmosis the most frequent infection at 13.2% (n=15), followed by neurocryptococcosis at 3.5% (n=4). The other infections included tuberculosis 0.9% (n=1), syphilis 0.9% (n=1), and non-specific meningitis 0.9% (n=1).

**TABLE 1 - Clinical and epidemiological characteristics of the patients.**

| Characteristics (total sample: 114) | Value | Percentage |
|---|---|---|
| Age (years) | | |
| mean (SD) | 46.7 (11.6) | |
| minimum-maximum age | 20-74 | |
| ≥40 years of age | 79 | 69.3 |
| Gender | | |
| male | 66 | 57.9 |
| Sexual orientation (self-reported) | | |
| heterosexual men | 50 | 43.8 |
| MSM | 16 | 14.0 |
| heterosexual women | 45 | 39.5 |
| Race/color | | |
| caucasian/white | 54 | 47.4 |
| *pardo*/brown | 44 | 38.6 |
| black | 16 | 14.0 |
| Education (years) | | |
| mean (SD) | 7.1 (3.7) | |
| minimum-maximum | 0-15 | |
| Smoking | | |
| yes | 68 | 59.6 |
| Alcohol consumption | | |
| yes | 81 | 71.1 |
| Illicit drug use | | |
| yes | 21 | 18.4 |

| Characteristics (total sample: 114) | Value | Percentage |
|---|---|---|
| Comorbidities | | |
| none | 57 | 50.0 |
| endocrine/metabolic | 30 | 26.4 |
| cardiovascular | 30 | 26.4 |
| osteoarticular | 3 | 2.6 |
| other diseases | 6 | 5.3 |
| ≥2 comorbidities | 22 | 19.3 |
| Time since diagnosis of HIV infection (years) | | |
| mean (SD) | 8.6 (5.7) | |
| minimum-maximum | 01-21 | |
| HAART >1 year | | |
| yes | 100 | 87.7 |
| Most recent CD4 | | |
| <200 cell/mm$^3$ | 9 | 7.9 |
| ≥200 cell/mm$^3$ | 105 | 92.1 |
| Most recent VL | | |
| <100,000 copies/ml | 112 | 98.2 |
| ≥100,000 copies/ml | 2 | 1.8 |
| Lowest past CD4 | | |
| <200 cell/mm$^3$ | 58 | 50.8 |
| ≥200 cell/mm$^3$ | 56 | 49.2 |
| Highest past VL | | |
| <100,000 copies/ml | 71 | 62.2 |
| ≥100,000 copies/ml | 37 | 32.4 |
| Duration of HAART treatment (years) | | |
| mean (SD) | 7.1 (5.5) | |

**SD:** standard deviation; **MSM:** men who have sex with men (other diseases: nephropathy or thyroid disease); **HIV:** human immunodeficiency virus; **HAART:** highly active antiretroviral therapy; **CD4:** cluster of differentiation 4 (CD4+ T lymphocyte count); **VL:** viral load **(**plasmatic viral load of HIV).

The mean time from HIV diagnosis until the evaluation was 8.6 ± 5.7 years (range 1-21 years). HAART was in use for >1 year in 87.7% (n=100) of the patients, with a mean treatment length of 7.0 ± 5.5 years. Undetectable VL were identified in 66.6% (n=76) of the patients, and 1.8% (n=2) had recent VL ≥100,000 copies/ml. The IHDS was applied in 111 patients. Three patients did not undergo evaluation because of the presentation of motor sequelae in the non-dominant hand; 53.2% (n=59) of the patients received a score of ≤10 and were therefore considered cognitively impaired. When the cutoff was changed to ≤11, with the goal to increase the detection sensitivity for milder or asymptomatic impairments, the percentage of individuals with neurocognitive impairment increased to 71.2% (n=79).

The mean DS score was 32.5 (range 2-72). This instrument was administered to 94 patients. Of the patients who did not complete the test, 6 patients were illiterate, 8 patients had visual deficits that compromised their ability to perform the test, and 6 patients could not perform the tasks following the given instructions. There was a significant positive correlation between education and performance on the DS (Pearson correlation coefficient=0.61, p<0.0001). The TGT was administered to 103 patients, with a mean score of 12.9 seconds (range 9-28). Eleven subjects did not perform the exam because of neurological or osteoarticular disease-related sequelae. All patients (n=114) completed the HAM-D17, and 26.3% (n=30) obtained scores >7, which is compatible with a depressive disorder. The IADL was administered to all patients; 68.4% (n=78) were classified as independent, whereas 31.6% (n=36) were classified as partially dependent. The CPE was ≥6 in 95% of the patients who underwent HAART for >1 year. The applied instrument results are shown in **Table 2**.

**TABLE 2 - Applied instrument results.**

| | Patients | |
|---|---|---|
| | n | % |
| International HIV Dementia Scale | 111 | |
| ≤10 | 59 | 53.2 |
| >10 | 52 | 46.8 |
| ≤11 | 79 | 71.2 |
| >11 | 32 | 28.8 |
| Digit Symbol Coding Test | 94 | |
| mean score (SD) | 32.5 (±14) | |
| minimum-maximum | 2-72 | |
| Timed Gait Test | 103 | |
| mean in seconds (SD) | 12.9 (±2.7) | |
| minimum-maximum | 9-28 | |
| Hamilton Rating Scale for Depression | 114 | |
| >7 (depressed) | 30 | 26.3 |
| ≤7 (not depressed) | 84 | 73.7 |
| Instrumental Activities of Daily Living Scale | 114 | |
| partially dependent | 36 | 31.6 |
| independent | 78 | 68.4 |
| CPE | 100 | |
| ≥6 | 95 | 95.0 |
| ≥7 | 76 | 76.0 |
| ≥8 | 64 | 64.0 |

**HIV:** human immunodeficiency virus; **SD:** standard deviation; **CPE:** Central Nervous System Penetration-Effectiveness Rank.

**Table 3** shows the variables associated with scores ≤10 on the IHDS compared with scores >10.

The prevalence of neurocognitive impairment was greater in the women compared with the men [66.7 versus 42.9%, respectively, p=0.01; odds ratio (OR) 2.66, 95% confidence interval (95% CI) 1.22-5.82]. When the prevalence of cognitive impairment (IHDS ≤10) was compared between the women aged <40 and ≥40 years, there was no significant difference (68.3 and 57.1%, respectively, p=0.67). Similarly, in men, the observed difference was not significant when the age groups of ≥40 and <40 years were compared (52.8 and 29.6%, respectively, p=0.07).

Neurocognitive impairment was more frequent in the patients aged ≥40 years compared with <40 years (61.0 versus 35.3%, OR 2.87; 95% CI 1.24-6.64).

The presence of co-morbidities (≥1) exhibited a significant association with neurocognitive impairment; thus, the patients with ≥1 co-morbidity more frequently exhibited an IHDS ≤10 compared with the patients without co-morbidities (64.3 versus 41.8%, respectively, p=0.02, OR 2.56, 95% CI 1.17-5.55). The presence of co-morbidities did not remain significant in the multiple regression analyses.

Previous low levels of CD4 were associated with an increased prevalence of neurocognitive impairment, and impairment was more common in individuals who had previously had a CD4 <200 cell/mm$^3$ (65.5 versus 41.1%, respectively, OR 2.71, 95% CI 1.25-5.86). Although the patients with a recent CD4 <200 cell/mm$^3$ more frequently exhibited an IHDS ≤10 compared with the patients with a recent CD4 >200 cell/mm$^3$, this association was not significant (88.8 versus 50%, respectively, OR 8.0, 95% CI 0.96-66.3).

Previous high VL levels were significantly associated with neurocognitive impairment as indicated by the IHDS. These changes were more common in individuals who had VL ≥100,000 copies/ml compared with the individuals with the highest VL <100,000 copies/ml (69.4 versus 46.4%, respectively, p=0.02; OR 2.62; 95% CI 1.12-6.16). The most recent VL levels were not associated with cognitive impairment.

Time since HIV diagnosis and time spent on HAART had no association with neurocognitive impairment.

In the multiple regression analysis, the independent variables associated with neurocognitive impairment identified by the IHDS were female gender (OR 3.31, 95% CI 1.33-8.22), education level (OR 1.24; 95% CI 1.08-1.41), and previous CD4 <200 cell/mm$^3$ (OR 2.65; 95% CI 1.09-6.39).

**TABLE 3 - Comparison of IHDS performance and clinical-demographic variables.**

| Variable | IHDS (n=114) | | | | | |
|---|---|---|---|---|---|---|
| | ≤10 | | >10 | | | |
| | n | % | n | % | P | OR (95% CI) |
| Gender | | | | | | |
| female | 32 | 66.7 | 16 | 3.3 | | |
| male | 27 | 42.9 | 36 | 57.1 | 0.01 | 2.66 (1.22-5.82) |
| Age (years) | | | | | | |
| ≥40 | 47 | 61.0 | 30 | 39.0 | | |
| <40 | 12 | 35.3 | 22 | 64.7 | 0.01 | 2.87 (1.24-6.64) |
| Comorbidities | | | | | | |
| none | 23 | 41.8 | 32 | 58.2 | | |
| ≥1 | 36 | 64.3 | 20 | 35.7 | 0.02 | 2.56 (1.17-5.55) |
| Most recent CD4 | | | | | | |
| <200 cell/mm$^3$ | 8 | 88.9 | 1 | 11.1 | | |
| ≥200 cell/mm$^3$ | 51 | 50.0 | 51 | 50.0 | 0.03 | 8.0 (0.96-66.3) |
| Most recent VL | | | | | | |
| <100,000 copies/ml | 58 | 53.2 | 51 | 46.8 | | |
| >100,000 copies/ml | 1 | 50.0 | 1 | 50.0 | 1.0 | 1.13 (0.06-18.6) |
| Lowest prior CD4 | | | | | | |
| <200 cell/mm$^3$ | 36 | 65.5 | 19 | 34.5 | | |
| ≥200 cell/mm$^3$ | 23 | 41.1 | 33 | 58.9 | 0.01 | 2.71 (1.25-5.86) |
| Highest prior VL | | | | | | |
| >100,000 copies/ml | 25 | 69.4 | 11 | 30.6 | | |
| <100,000 copies/ml | 32 | 46.4 | 37 | 53.6 | 0.02 | 2.62 (1.12-6.16) |
| | Mean (SD) | | Mean (SD) | | P | Mean difference |
| Age (years) | 49.9 (10.75) | | 43.42 (12.0) | | 0.004 | 6.47 (2.16-10.78) |
| Education (years) | 5.86 (3.42) | | 8.65 (3.50) | | <0.001 | -2.78 (-4.09, -1.48) |
| Time since diagnosis of HIV infection (years) | 8.59 (5.37) | | 8.71 (6.37) | | 0.91 | |

**IHDS:** International HIV Dementia Scale; **OR:** odds ratio; **95% CI:** 95% confidence interval; **CD4:** cluster of differentiation 4; **lowest CD4:** lowest count of CD4+ T lymphocytes; **VL:** viral load; **highest VL:** highest previous viral load; **SD:** standard deviation.

**Table 4** shows the comparison between the performances on the IHDS and the other instruments.

The mean score obtained from the DS was 26.3 for the patients with an IHDS ≤10 and 39.5 for the patients with an IHDS >10 (p<0.001; mean difference -13.19; 95% CI -18.28, -8.11).

On the TGT, the mean time for the patients with an IHDS ≤10 was greater than the mean time obtained by the patients with an IHDS >10 (13.81±3.25 versus 11.96 ± 1.73, respectively, p=0.001; mean difference 1.85; 95% CI 0.80-2.89).

Among the patients with an IHDS ≤10, 50.8% (n=30) were considered partially dependent based on the IADL performance, and 7.7% (n=4) of the patients with an IHDS >10 were considered partially dependent (OR 12.41; 95% CI 3.96-38.83).

No association was identified between the CPE and neurocognitive impairment.

This study failed to identify an association between depression and neurocognitive impairment (p=0.054; OR 2.45; 95% CI 0.99-6.01).

## DISCUSSION

Based on 111 patients evaluated via the IHDS, 53.2% (n=59) had scores ≤10 and a potential diagnosis of HAND. This figure is similar to the results reported by Rodrigues et al. in the study that validated the IHDS in Brazil[9]. However, the percentage is less than the higher prevalence rates reported in

**TABLE 4 - Comparison of IHDS performance in relation to other instruments.**

| Variable | Patients (n) | IHDS | | | | P | OR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | ≤10 | | >10 | | | |
| | | n | % | n | % | | |
| HAM-D17 | 114 | | | | | | |
| >7 (depressed) | | 20 | 69.0 | 9 | 31.0 | | |
| ≤7 (not depressed) | | 39 | 47.6 | 43 | 52.4 | 0.05 | 2.45 (0.99-6.01) |
| IADL | 114 | | | | | | |
| partial dependence | | 30 | 88.2 | 4 | 11.8 | | |
| independence | | 29 | 37.7 | 48 | 62.3 | <0.001 | 12.41 (3.96-38.83) |
| | | Mean (SD) | | Mean (SD) | | P | Mean difference |
| Digit Symbol-Coding Test | 94 | | | | | | |
| mean score (SD) | | 26.33 (11.56) | | 39.52 (12.94) | | <0.001 | -13.19 (-18.28-8.11) |
| Timed Gait Test | 103 | | | | | | |
| mean time (SD) | | 13.81 (3.25) | | 11.96 (1.73) | | 0.001 | 1.8 (2.89-0.80) |

**IHDS:** International HIV Dementia Scale; **OR:** odds ratio; **95% CI:** 95% confidence interval; **HAM-D17:** 17-item Hamilton Rating Scale for Depression; **IADL:** Instrumental Activities of Daily Living Scale; **SD:** standard deviation.

other countries[3,11,19]. In Switzerland, Simioni et al.[11] utilized a complex battery of neuropsychological exams and evaluated 100 HIV patients who underwent HAART with undetectable VL. The researchers reported a 69% prevalence of neurocognitive disorders. A similar prevalence (64.4%) was reported by Nakku et al.[30], who evaluated the frequency of neurocognitive impairment in 680 HIV patients in Uganda using the IHDS as the instrument of measure.

When we used the strategy described by Rodrigues et al.[9] of shifting the cutoff point of the IHDS to ≤11 to increase the sensitivity up to 75.7% for the detection of less severe neurocognitive impairment, we identified a prevalence of 71.2% (n=79) in our patients; these findings are more consistent with the previously reported literature[11,30].

Differences in the prevalence identified in previous studies may be explained by the diversity of instruments used, differences in the patterns of performance among different populations, or the lack of controlling variables capable of influencing neuropsychological test results, such as the education level, unemployment, and depression[3]. Factors directly related to HIV infection can also justify the described differences in the prevalence rates; the predictive factors of HAND, such as low CD4 and high VL levels, tend to be more frequent in vulnerable populations in which a diagnosis is often delayed by a lack of access to health services or knowledge regarding the infection. For example, in countries such as Brazil, the use of HAART for patients with CD4 >500 cell/mm$^3$ has only recently been widely applied[31].

The IHDS was developed as a screening tool for the neurocognitive disorders present in HIV-infected patients, and its use has been recommended by international guidelines[7,8,32,33]. Although it is not sufficient to fulfill the current proposed criteria for HAND[32], a recent study regarding the validation of the instrument in Brazil[9], which used a cutoff value of ≤10, indicated a sensitivity of 78.5% and specificity of 80.8% for HIV-associated dementia and a sensitivity of 55% and specificity of 80% for all forms of HAND; thus, this cutoff was useful to exclude neurocognitive impairment and identify the patients who required specialized evaluation[9].

Considering the lack of formal neuropsychological evaluation in the study location, as well as the aim of reinforcing the hypothesis that neurocognitive impairment identified using the IHDS could be related to HIV, we compared patient performances on the IHDS with the performances on the other tests designed to assess subcortical functions. A significant association was identified when the IHDS was compared with the TGT and DS results. These findings are consistent with previous studies. In Kenya, Kwasa et al.[34] used the IHDS, Mini-Mental State Examination, and neuropsychological tests to evaluate different cognitive domains in HIV+ patients and identified the worst TGT performances among individuals with neurocognitive impairment[34]. Similarly, Lawler et al.[33] evaluated 120 patients in Botswana and determined that individuals classified with neurocognitive impairment using the IHDS had lower scores on the DS (30.4 'without alterations in the IHDS versus 41.7 with alterations; p<0.001)[33]. The researchers also noted that education and neurocognitive impairment defined using the IHDS were the variables associated with performance on the DS[33]. Our study also evaluated the education levels alongside the DS performance. A significant positive correlation between the variables was identified, with test performances improving with increasing years of education (p<0.0001).

Given the involvement of the cerebral basal ganglia, periventricular white matter, and hippocampus, HAND create

lesions associated with peculiar clinical manifestations, such as bradykinesia (slowing of body movement) and bradyphrenia (slowing of mental processing with consequent impairments in learning and memory). The motor retardation is characterized by the diminishment of gait speed and oppositional movement of the fingers. The impairment of functions related to learning and memory primarily affects the components of recognition, registration, and recall[35] [36]. The TGT and DS, which assess these functions, respectively, exhibited significant correlations with the IHDS performance. Although these tests should not be used separately as a substitute for the IHDS, each test evaluates a unique cognitive domain, and these significant correlations suggest that neurocognitive impairment may be related to HIV.

In the univariate analysis, the variables that exhibited a significant association with neurocognitive impairment were age, female gender, education level, presence of co-morbidities, CD4 <200 cells/mm$^3$ and VL >100,000 copies/ml. These findings are consistent with previously published findings. A longitudinal cohort study in Canada conducted by McCombe et al.[16] identified advanced age as a predictor of HAND. In a multivariate analysis, the authors demonstrated that for each additional year of age after 18 years, there was an increase of 3.2% in the risk of HAND development. The authors also identified an association between HAND and low CD4, high VL, and duration of HIV infection[16].

The prevalence of women with neurocognitive impairment in our study was 66.7% compared with 42.9% for men, which was significantly different (OR 2.66; 95% CI 1.22-5.82). In a stratified analysis by the age groups <40 and ≥40 years, there was no interaction between gender and IHDS performance. Social income variables were not evaluated; however, female gender and education level remained independently associated with neurocognitive impairment. The literature is conflicting regarding the association between gender and HAND. Some authors suggest that different domains are impaired in men and women. Women, in general, have fewer years of schooling, experience less favorable socioeconomic conditions, are more often exposed to alcohol and substance abuse, and exhibit a higher prevalence of psychiatric disorders, all of which are factors related to poor performance on neuropsychological tests[37] [38] [39].

Our study also identified an association between the recent and previous CD4 levels and neurocognitive impairment, with lower CD4 counts in patients with an IHDS ≤10; however, only a previous CD4 <200 cell/mm$^3$ remained significant in the multivariate analysis. These results corroborate previous findings that have demonstrated an association between HAND and CD4 nadir[16] [40].

Our data indicate an association between previous VL >100,000 copies/ml and the presence of neurocognitive impairment, although not as an independent variable. These results are consistent with previous studies[16]. Increased VL is associated with higher levels of viral copies in the CNS, which could theoretically result in greater neurological damage[41].

The prevalence of depressive disorders in the studied patients was 26.3% (n=30) using the HAM-D17 with a cutoff point of >7. Depression has been reported to be more prevalent in HIV+ individuals compared with the general population and ranges from 12 to 66%[18] [19]. This variability of reported rates can, at least in part, be explained by the variation in measures and cutoff points used in different localities or the availability of tests validated for these measurements[19]. Our results are similar to other studies conducted in Brazil[13] [19] [42].

In the multiple regression analysis, female gender, education level, and prior CD4 <200 cells/mm$^3$ remained significantly and independently associated with neurocognitive impairment.

No association was identified between the CPE and neurocognitive impairment. The substantial diversity in the HAART regimens used by the patients may have influenced the results.

The patients with an IHDS ≤10 were more likely to be partially dependent than the patients without impairment (OR 12.4; 95% CI 3.9-38.8). Although the study design did not enable the directionality of this association to be determined, these data indicate the impact of neurocognitive impairment on the individuals' daily lives[23].

This study comprises one of the first studies to assess the prevalence of neurocognitive impairment in a Brazilian population; thus, it possesses several limitations. The absence of a control group prevented a comparison of the prevalence with an HIV-negative population. The lack of neuropsychological evaluations did not permit the identification of disorders using the IHDS compared with the gold standard as suggested by the literature[32]. Finally, our sample is small compared with international studies, which may have influenced the assessment of variables previously described to be predictors of HAND, such as the duration of infection, age, VL, and depression. However, this study reflects the reality of many Brazilian outpatient services, and perhaps the reality in other developing countries, in which the shortage of human and financial resources prevents the use of all recommended neuropsychological evaluations, but considers it essential to identify patient groups potentially affected by neurocognitive disorders.

The prevalence of neurocognitive impairment in individuals with HIV/AIDS in outpatient care was high. The use of IHDS scores ≤10 as diagnostic criteria and the correlations between the IHDS results and the TGT and DS results suggest that the alterations in question may be related to HIV after the cognitive domains evaluated by these tests are overtly affected during the course of infection. We identified a significant and independent association between neurocognitive impairment and female gender, education level, and previous CD4 <200 cell/mm$^3$.

The high prevalence of depression and neurocognitive impairment in individuals with HIV/AIDS alerts practitioners to the need to actively identify these diagnoses. In addition, the high frequency of patients with partial dependency in their daily activities among patients with neurocognitive impairment suggests the need to track these changes in HIV+ outpatients.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## REFERENCES


1. Seidl EMF, Melchíades A, Farias V, Brito A. Pessoas vivendo com HIV/AIDS: variáveis associadas à adesão ao tratamento anti-retroviral. Cad Saude Publica 2007; 23:2305-2316.
2. Peters BS, Conway K. Therapy for HIV: past, present, and future. Adv Dent Res 2011; 23:23-27.
3. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol 2011; 17:3-16.
4. Du Pasquier R, Cavassini M, Simioni S, Annoni JM, Giacobini E, Hirschel B. Nouveau spectre de troubles cognitifs liés à l'infection par le VIH à l'ere des trithérapies. Rev Med Suisse 2009; 5:955-966.
5. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. Lancet Infect Dis 2013; 13:976-986.
6. Lindl KA, Marks DR, Kolson DL, Jordan-Sciutto KL. HIV-associated neurocognitive disorder: Pathogenesis and therapeutic opportunities. J Neuroimmune Pharmacol 2010; 5:294-309.
7. Sacktor NC, Wong M, Nakasujja N, Skolasky RL, Selnes OA, Musisi S, et al. The International HIV Dementia Scale: a new rapid screening test for HIV dementia. AIDS 2005; 19:1367-1374.
8. Group MEW. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. Clin Infect Dis 2013; 56:1004-1017.
9. Rodrigues RA, Oliveira RL, Grinsztejn B, Silva MT. Validity of the International HIV dementia scale in Brazil. Arq Neuropsiquiatr 2013; 71:376-379.
10. Chan LG, Kandiah N, Chua A. HIV-associated neurocognitive disorders (HAND) in a South Asian population - contextual application of the 2007 criteria. BMJ Open 2012; 2:e000662.
11. Simioni S, Cavassini M, Annoni JM, Rimbault Abraham A, Bourquin I, Schiffer V, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS. 2010; 24:1243-1250.
12. Gisslén M, Price RW, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? BMC Infect Dis 2011; 11:356.
13. Fernandes Filho SM, de Melo HR. Frequency and risk factors for HIV-associated neurocognitive disorder and depression in older individuals with HIV in northeastern Brazil. Int Psychogeriatr 2012; 24:1648-1655.
14. de Almeida SM, Ribeiro CE, de Pereira AP, Badiee J, Cherner M, Smith D, et al. Neurocognitive impairment in HIV-1 clade C- versus B-infected individuals in Southern Brazil. J Neurovirol 2013; 19:550-556.
15. Letendre S. Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. Top Antivir Med 2011; 19:137-142.
16. McCombe JA, Vivithanaporn P, Gill MJ, Power C. Predictors of symptomatic HIV-associated neurocognitive disorders in universal health care. HIV Med 2013; 14:99-107.
17. Robertson K, Liner J, Heaton R. Neuropsychological assessment of HIV-infected populations in international settings. Neuropsychol Rev 2009; 19:232-249.
18. Hinkin CH, Castellon SA, Atkinson JH, Goodkin K. Neuropsychiatric aspects of HIV infection among older adults. J Clin Epidemiol 2001; 54 (suppl I):44-52.
19. Silveira MPT, Guttier MC, Pinheiro CA, Pereira TV, Cruzeiro AL, Moreira LB. Depressive symptoms in HIV-infected patients treated with highly active antiretroviral therapy. Rev Bras Psiquiatr 2012; 34:162-167.
20. Bragança M, Palha A. Depression and neurocognitive performance in Portuguese patients infected with HIV. AIDS Behav 2011; 15:1879-1887.
21. Elliott AJ, Russo J, Roy-Byrne PP. The effect of changes in depression on health related quality of life (HRQoL) in HIV infection. Gen Hosp Psychiatry 2002; 24:43-47.
22. Moosa MYH, Jeenah FY. Treating depression in HIV-positive patients affects adherence. S Afr J HIV Med 2012; 13:144-149.
23. Gorman AA, Foley JM, Ettenhofer ML, Hinkin CH, van Gorp WG. Functional consequences of HIV-associated neuropsychological impairment. Neuropsychol Rev 2009; 19:186-203.
24. Moreno RA, Moreno DH. Escalas de depressão de Montgomery & Åsberg (MADRS) e de Hamilton (HAM-D). Rev Psiq Clin 1998; 25:262-272.
25. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry 1988; 45:742-747.
26. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179-186.
27. Santos RL, Virtuoso Júnior JS. Confiabilidade da versão brasileira da escala de atividades instrumentais da vida diária. Rev Bras Promoç Saude 2008; 21:290-296.
28. Kreiner DS, Ryan JJ. Memory and motor skill components of the WAIS-III Digit Symbol-Coding subtest. Clin Neuropsychol 2001; 15:109-113.
29. Robertson KR, Parsons TD, Sidtis JJ, Hanlon Inman T, Robertson WT, Hall CD, et al. Timed Gait test: normative data for the assessment of the AIDS dementia complex. J Clin Exp Neuropsychol 2006; 28:1053-1064.
30. Nakku J, Kinyanda E, Hoskins S. Prevalence and factors associated with probable HIV dementia in African population: A cross-sectional study of an HIV/AIDS clinic population. BMC Psychiatry 2013; 13:126.
31. Ministério da Saúde. Protocolo clínico e diretrizes terapêuticas para manejo da infecção pelo HIV em adultos. Brasília, 2013. Cited 2014 Sept 11. Available at: http://www.aids.gov.br/sites/default/files/anexos/page/2014/56425/_p_protocolo_21_08_2014_pdf_p__18858.pdf
32. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007; 69:1789-1799.
33. Lawler K, Mosepele M, Ratcliffe S, Seloilwe E, Steele K, Nthobatsang R, et al. Neurocognitive impairment among HIV-positive individuals in Botswana: a pilot study. J Int AIDS Soc 2010; 13:15-23.
34. Kwasa J, Cettomai D, Lwanya E, Osiemo D, Oyaro P, Birbeck GL, et al. Lessons learned developing a diagnostic tool for HIV-associated dementia feasible to implement in resource-limited settings: pilot testing in Kenya. PLoS One 2012;7:e32898.
35. Woods SP, Moore DJ, Weber E, Grant I. Cognitive neuropsychology of HIV-associated neurocognitive disorders. Neuropsychol Rev 2009; 19:152-168.
36. Dickson DW. Neuropathology of non-Alzheimer degenerative disorders. Int J Clin Exp Pathol 2009; 3:1-23.
37. Faílde-Garrido JM, Alvarez MR, Simón-López MA. Neuropsychological impairment and gender differences in HIV-1 infection. Psychiatry Clin Neurosci 2008; 62:494-502.
38. Hestad KA, Menon JA, Silalukey-Ngoma M, Franklin Jr DR, Imasiku ML, Kalima K, et al. Sex differences in neuropsychological

performance as an effect of human immunodeficiency virus infection: a pilot study in Zambia, Africa. J Nerv Ment Dis 2012; 200:336-342.

39. Steinberg TC. Predictors of HIV-related neurocognitive impairment in an HIV/Aids population (dissertation). Denton, Texas. University of North Texas Digital Library, 2012. 119p. Accessed 2014 Sept 11. Available at: http://digital.library.unt.edu/ark:/67531/metadc149667/

40. Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS 2011; 25:1747-1751.

41. Ciccarelli N, Fabbiani M, Colafigli M, Trecarichi EM, Silveri MC, Cauda R, et al. Revised central nervous system neuropenetration-effectiveness score is associated with cognitive disorders in HIV-infected patients with controlled plasma viraemia. Antivir Ther 2013; 18:153-160.

42. Mello VA, Segurado AA, Malbergier A. Depression in women living with HIV: clinical and psychosocial correlates. Arch Womens Ment Health 2010; 13:193-199.