High prevalence of HIV-associated neurocognitive disorders (HAND) in São Paulo City, Brazil

Alta prevalência de desordem neurocognitiva associada ao HIV (HAND) na Cidade de São Paulo, Brazil

Maria R Gascon[1,2], Mayra Lima[1], Priscila M. Cheutchuk[2], Eduardo A. Oliveira[2], Giovana S. de Oliveira[2], Carolina Fernandes Gualqui[2], Luiz A. M. Fonseca[1], Marcello Magri[1], Mauricio D. Ferreira[1], Ana Paula R. Veiga[1], Mariana A. Monteiro[1], Yuyang Tang[3], Guochun Jiang[3], Alberto JS Duarte[1], Lucette Cysique[4] and Jorge Casseb[1]*, and on the behalf of the HIV outpatient clinic - Secondary Immunodeficiencies Service (ADEE3002).

ABSTRACT

Introduction: HIV-associated neurocognitive disorders (HAND) are the subject of many studies, some of them reporting a prevalence of up to 50 percent. **Objectives:** To determine the prevalence and factors associated with HIV neurocognitive disorders (HAND) in a cohort of HIV-1-infected patients in São Paulo city, Brazil. **Methodology:** Descriptive cross-sectional study including 106 HIV-1-infected patients, employing direct interview and neuropsychological tests, applied by trained neuro-psychologists with expertise in the tests. Other, similar assessment tools we used were Brief Neurocognitive Questionnaire, International HIV Dementia Scale, Lawton Instrumental Activities of Daily Living, Hospital Anxiety and Depression Scale, Social Support Scale for People with HIV/Aids, Assessment of Adherence to Antiretroviral Therapy Questionnaire, and a complex neuropsychological assessment. Results: We included 106 patients from May 2015 to April 2018. We found a high prevalence of HAND in our patients (45%), with 27.5% presenting asymptomatic neurological impairment (ANI) and 17.5% mild neurological dysfunction (MND); only one patient presented HIV-associated dementia (HAD) (0.9%). Women were more likely to have MND (52.9%) and the only case of HAD was also female. The high prevalence of neurocognitive disorders was independent of the immunological status, use of efavirenz, or virological control. **Conclusions**: This study may mirror the national and international scenarios, showing a high prevalence of HAND (45%) and the prevalence of some risk factors, in special among women.

Key word: HIV; HIV-neurocognitive associated disorder (HAND); HIV-associated dementia (HAD), Brazil.

RESUMO

Introdução: As doenças neurocognitivas associadas ao HIV (HAND), são o assunto de muitos estudos, alguns deles relatando uma prevalência de até 50 por cento. **Objetivos:** Determinar a prevalência e os fatores associados aos distúrbios neurocognitivos do HIV (HAND) em uma coorte de pacientes infectados pelo HIV-1 na cidade de São Paulo, Brasil. **Metodologia:** Estudo transversal descritivo incluindo 106 pacientes infectados pelo HIV-1, utilizando entrevista direta e testes neuropsicológicos, aplicados por neuropsicólogos treinados com experiência nos testes. Foram utilizados também: Questionário Neurocognitivo Breve, Escala Internacional de Demência do HIV, Atividades Instrumentais de Vida Diária de Lawton, Escala Hospitalar de Ansiedade e Depressão, Escala de Apoio Social para Pessoas com HIV / Aids, Avaliação da Adesão à Terapia Antiretroviral Questionário e uma bateria de avaliação neuropsicológica complexa. Resultados: Foram avalaidos 106 pacientes de maio de 2015 a abril de 2018. Foi observado uma alta prevalência de HAND em nossos pacientes (45%), com 27,5% apresentando comprometimento neurológico assintomático (ANI) e 17,5% comprometimento cognitive leve (MND); apenas um paciente apresentou demência associada ao HIV (DAH) (0,9%). As mulheres eram mais propensas a ter MND (52,9%) e o único caso de HAD também era do sexo feminino. A alta prevalência de distúrbios neurocognitivos foi independente do estado imunológico, uso de efavirenz ou controle virológico. **Conclusões:** Este estudo pode espelhar o cenário nacional e internacional, mostrando uma alta prevalência de HAND (45%) e a prevalência de alguns fatores de risco, em especial entre as mulheres.

Palavras-chave: HIV; Transtorno neurocognitivo associado ao HIV (HAND); Demência associada ao HIV (HAD), Brasil.

1.HIV Outpatient Clinic - Secondary Immune-deficiencies Service (ADEE3002). Department of Dermatology of Hospital das Clínicas, University of São Paulo Medical School. ADEE3002 – Department of Dermatology, Hospital das Clinicas, São Paulo University, São Paulo; 2.Department of Psychology, Hospital das Clínicas, São Paulo University Medical School, São Paulo, Brazil; 3.UNC HIV Cure Center, Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill, North Carolina US 27599; 4.Sydney St. Vincent's Hospital Centre for Applied Medical Research | Senior researcher.

Corresponding author: Jorge Casseb, MD. Department of Dermatology, 255. Av. Dr. Eneas de Carvalho Aguiar, 3rd floor, São Paulo, Brazil. E-mail address: jcasseb@usp.br and/or Alternative author: M.R. Gascon, LIM56, 500 Av. Dr. Eneas de Carvalho Aguiar, 3rd floor, São Paulo, Brazil. Zip code: 01246-000. E-mail address: mariaritapolo@yahoo.com.br.

Funding statement: Support: FAPESP n. 2018/07239-2; CNPq: nº 301275/2019-0; and Scholarship from FM/FMUSP, and UNC CFAR Developmental Award (P30 AI50410) and NIH CARE (1UM1AI126619) to GJ.

Declaration of author competing interests: The authors declare that there is no conflict of interest.

INTRODUCTION

Human immunodeficiency virus type 1 (HIV-1) infection remains a global public health problem (1). The introduction of combined antiretroviral therapy (cART) turned AIDS a chronic disease amenable to control, reducing morbidity and death. Although good adherence to cART provides effective plasma viral suppression, the rates of HIV-associated neurocognitive disorders (HAND) are increasing, especially in their milder forms (2-6), and in developing countries, such as Brazil (9).

The profile of neurocognitive manifestations among people living with HIV (PLWH) changed dramatically in the ART era, characterized by a reduced incidence of HIV Associated Dementia (HAD) but increased Mild Neurocognitive Disorder (MND) and Asymptomatic Neurocognitive Impairment (ANI) (1). Currently, prevalence is estimated between 15-30% for ANI, 20-50% for MND and 2-8% for HAD (1,2,8). These proportions are constant regardless of the location of the studies, as many as half of those infected with HIV in Europe and the US may have some degree of cognitive impairment, predominantly asymptomatic (5). In Brazil, it has been already shown that the prevalence of HAND ranges from 4.6% to 52.4% (7), while In Latin America the prevalence of HAND varies from 26.8% to 45%.(8-10). However, most data come from countries with distinct characteristics, particularly those regarding the level of education and income (8-17). Here we aimed to identify the prevalence of HAND in a cohort of HIV-1-infected subjects with high adherence to cART, HIV replication under control and low prevalence of opportunistic diseases, as reported previously (15).

METHODS

This study was carried out with outpatients from Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC), between May 2015 and April 2018. One-hundred and six patients were selected according to inclusion and exclusion criteria. The inclusion criteria included presence of HIV antibodies in serum (ELISA and Western Blot), age older than 18 years, at least four years of formal education, being in use of cART and in regular medical follow-up over the last year and ability to understand and sign an informed consent form. The exclusion criteria were: prior or current diagnosis of documented neurological conditions (traumatic, metabolic, vascular or degenerative) that might interfere with the cognitive performance assessment, co-infection (e.g. HCV, HBV and HTLV), use of psychoactive substance, and inability to understand essential content for neuropsychological evaluation. The study was approved by The Ethical Board of the Hospital (Cappesq number 982.307) and an informed signed consent was obtained from all participants prior to study inclusion, who signed and took home one form also signed by the investigator.

The assessment tools we used were: sociodemographic questionnaire, Brief Neurocognitive Questionnaire, International HIV Dementia Scale (IHDS) (18), Lawton Instrumental Activities of Daily Living (19), Hospital Anxiety and Depression Scale (HADS) (20), ASSIST - Screening with alcohol, tobacco and other substances (21), Social Support Inventory for People Who Are Positive or Have Aids (22), CEAT-VIH - Assessment of Adherence to Antiretroviral Therapy Questionnaire (23), and a complete neuropsychological battery (24-26). All volunteers were submitted to the same batteries of neurological tests, performed by the same team (MRG and CFG) at the same clinical site, in an office exclusive for this activity. The investigators were blinded for the HIV serostatus and the same battery was used throughout the entire study. One extra visit was scheduled to disclose tests results. Two patients with dementia had their relatives participating in the appointment for help with the evaluation.

We determined patients neuropsychological profile by complex neuropsychological assessment, consisting of the following instruments: Memory: Operating and Working – Digits (24), Episodic Auditory - The Rey Auditory-verbal learning test (RAVLT) (25); Speed Information Processing: Codes (24); Executive Function: Phonemic Verbal Fluency Test (FAS) and Categorical Verbal Fluency (Animal Naming) (26), - Trail Making Test A and B (26); and Motor Skills: Grooved Pegboard (26). After neuropsychological assessment, patients were classified according to HAND categories adapted from the American Academy of Neurology, also known as Frascati's Criteria (3).

We extracted clinical, laboratory and demographical data from the electronic medical records (PRONTMED) and/or from direct interview, previously to the neuropsychological test application. HIV viral load and T-CD4 cells count were performed at the laboratory of the Hospital (27). We checked cART regimens using the Hospital pharmacy database (SIGH, Prodesp). We gave special attention to efavirenz use due to the possibility of neurological side effects, which might affect patient's performance on neuropsychological tests.

1.1. Statistical Analysis

We created a database with our data and displayed our results in frequency tables. For the neuropsychological performance comparison among groups we performed analysis of variance for independent samples with one factor (one-way ANOVA), to identify potential covariates associated with the participants' neuropsychological performance (gender, age, education and depression). After the establishment of the variables, an analysis of three groups was performed (ANCOVA) to eliminate the effect of those co-variates. We used Mann-Whitney test after Kolmogorov-Smirnov normality test, and Bonferroni´s Post-Hoc test, to identify statistical differences in pairs of groups. We performed all quantitative analyses with the aid of the statistical package SPSS (21.0); we set $p < 0.05$ as the significance level.

RESULTS

We studied 24.6% of our active patients (106 of the

430 subjects who comprise the whole cohort). Table 1 shows the demographic characteristics of the three groups of neurocognitive impairment. HIV-1-infected subjects were predominantly male (n = 79, 74.5%), single (n = 51, 48.1%), their mean age was 46.36 years (SD ± 11.93), their mean schooling was 12.32 years (± 3.67) and 89.5 percent were employed at the time of the evaluation; there were no difference for those variables. Criteria for HAND classification indicated that 49 men (46.2%) and 8 (7.5%) women had a normal cognitive performance ; 32 patients (30.2%) had ANI, 22 (20.7%) of whom were men and 10 (9.4%) were women; 17 (16%) had MND, 8 (7.5%) of whom were men and 9 (8.4%) were women. One patient (a woman) had a diagnosis of HAD (0.9%), but failed to complete most of the neuropsychological tests of the evaluation battery, and was excluded from further analysis.

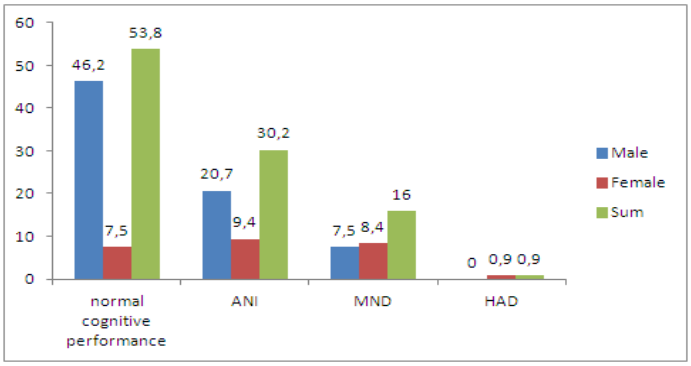
Table 1. Characterization of the 106 HIV-infected participants in relation to age, gender, education level, marital status and occupation.

Variable	Category	Normal (n=57)	ANI (n=32)	MND (n=17)	P value
Gender	Male	49 (85.9%)	22 (68.75%)	8 (47.0%)	0.004
	Female	8 (14.0%)	10 (31.2%)	9 (52.9%)	
Age*		45.70(±11.7)	43.72 (±12.7)	46 ±12	0.47
Educational level*		13.20 (±4.0)	12.7 (±4.0)	11 ± 4	0.37
Marital status	Single	34 (59.6%)	13 (40.6%)	4 (23.5%)	0.26
	Married	17 (29,8%)	15 (46,9%)	10 (58,8%)	
	Divorced	4 (7.0%)	1 (3.1%)	2 (11.7%)	
	Widower	2 (3.5%)	3 (9.3%)	1 (5.8%)	
Occupation	Home	1 (1.7%)	1 (3.1%)	1 (5.8%)	0.29
	Employee	51 (89,5%)	25 (78,1%)	10 (58.8%)	
	Unemployee	2 (8.7%)	4 (22.2%)	5 (29.4%)	
	Retiree	3 (13%)	2 (11.1%)	1 (5,9%)	

Notes: P value <0.05 (T-Mann-Whitney after Kolmogorov-Smirnov normality test); SD = standard deviation. One case with HIV-associated dementia (HAD) was not present here.
ANI: Asymptomatic; MND: Mild neurocognitive Disease

In summary, from 27 women (100%) who completed the entire evaluation, 8 (29.6%) had a normal performance, 10 (37%), had ANI, and 9 (33.3%) had MND. Including the patient who had HIV-associated dementia (HAD), a total of 20 women had HAND, or 71.4%. In contrast, among 79 men, 49 (62%) presented normal performance, 22 (27.8%) had ANI, and 8 (10.1%) had MND, the total of men who had HAND reaching 30 (38%). A comparison of the genders' proportions,was significant (p=0.001).

Graph1: Distribution of HAND frequency according to sex.



In the distribution of cognitive changes among people living with HIV (PLWH), the higher frequency of women with the MND form (33.3%), when compared to men (10.1%), deserves attention. Pearson's correlation showed that years of schooling (rho = -0.511 and p = 0.002) was associated with the outcome, that is,, the lower the schooling the more severe the HAND. Other variables did not reach statistical significance, such as age (p = 0.268), systemic diseases (p = 0.952) like diabetes (n = 10), hypertension (n=14) and dyslipidemia (n= 19); duration of the infection (p = 0.09, mean: 18.40 ± 7.95 years), CD4+ T cell count (p = 0.52, 751 ± 366 cells/mm3) and plasma HIV RNA viral load (p = 0.815) also were not associated with the outcome. Only eight patients (7.5%) had a detectable viral load (median <200 copies/mL), but no association with HAND was found (Table 2). We did not find association of anxiety and depression with HIV status. Although there was no significant difference, we did observe that MND forms had a lower score on the compliance scale (CEAT), the main reason being forgetfulness in relation to taking medications and also showing less emotional support (Table 3). As a rule patients showed a poor performance in the following tests: digits, episodic memory of immediate recall, post-interference and late, Trail A and B, FAS and Animals, Grooved dominant hand, namely short-term memory, episodic memory of immediate recall, post interference, sustained and alternating attention, phonetic and categorical verbal fluency, and dominant hand speed, whereas in the following tests: codes and non-dominant hand grooved, that is, in cognitive functions of speed of processing and motor speed results were better (Table 4). Women performed worse than men in digits (p = 0.01), trail making A (p = 0.03) and grooved pegboard non-dominant hand (p = 0.03). In addition, women showed

more impairment than men in working memory, sustained attention and non-dominant hand motor speed. There was no statistical difference regarding anxiety (p = 0.52) and depression (p = 0.82), which may influence performance. Age (p = 0.90) and education (p = 0.08) variables were also not statistically different.

Table 2. Distribution of laboratory data through HAND categories

Variable	Normal (57)	ANI (32)	MND (17)	p value
CD4+ T count (cells/mm3)	693 ± 293	741 ± 310	707 (±340)	0.82
HIV RNA plasma viral load				
Undetectable	51 (89.4%)	30 (93.7%)	14 (82.3%)	0.46
Detectable	6 (10.5%)	2 (6.2%)	3 (17.6%)	
Efavirenz				
Use	23 (40.3%)	8 (44.4%)	6 (42.8%)	
No use	34 (59.6%)	10 (55.5%)	8 (57.1%)	0.36

*= n (%). p<0.05. Undetectable plasma viral load <40 copies/ml; American Academy of Neurology 2007 - Frascati Criteria for HAND.

Table 3. Emotional, cART adherence and social support of the patients assessed through the categories HAND.

Scales	Normal (57)	ANI (32)	MND (16)	P value
Depression and Hospital Anxiety Scale A	6.18 ± 4.64)	5.45 ± 9.47	9.47 ± 4.30	0.04*
Depression and Hospital Anxiety Scale D	5.16 ± 4.39	4.97 ± 4.60	8.12 ± 3.80	0.03*
Questionnaire assessing adherence to antiretroviral treatment (CEAT)	82.00 ± 8.31	79.78 ± 7.36	77.2 ± 8.02	0.08
Instrumental Social Support	42.51 ± 13.7	44.1 ± 9.52	41.41 ± 11.43	0.73
Emotional Social support	44.96 ± 11.48)	46.12 ± 9.23	38.82 ± 13.52	0.08

Notes: CEAT: Questionnaire assessing adherence to antiretroviral treatment; ISS: Instrumental and Emotional Social Support, Social Support Scale for People Living with HIV/AIDS. HAND: American Academy of Neurology 2007 - Frascati Criteria. Each scale was 1:100.

Table 4. Distribution of mean percentiles of each neuropsychological battery test distributed according to HAND categories.

Tests	Normal (n.57)	ANI (n.32)	MND (n.17)	P value	Post Hoc
Memory					
Digit Span	60.33 ± 24.45)	52.59 ± 26.18	41.11 ± 26.15	0.029*	B
RAVLT – IM	35.93 ± 24.76)	17.83 ± 18.61	12.48 ± 15.9)	<0.001*	A e B
RAVLT – PI	38.20 ± 24.63)	21.32 ± 22.31)	19,70 ± 18.93	0.001*	A e B
RAVLT – TR	37.18 ± 24.8	16.33 ± 20.42)	14.81 ± 16.41	<0.001*	A e B
RAVLT – RC	11.45 ± 3.9	10.9 ± 3.04	8.31 ± 5.7	0.001*	A e B
Attention					
Trail Making A	51.98 ± 29.66)	35.30 ± 29.66	24.78 ± 23.66	0.001*	A e B
Trail Making B	52.77 ± 25.81	24.68 ± 29.06	20.55 ± 30.78	<0.01*	A e B
Processing Speed					
Digit Symbol Coding	69.78 ± 20.50)	53.71 ± 27.65	53.31 ± 30.59	0.005*	A
Executive Function					
F.A.S.	39.18 ± 26.84	23.06 ± 22.91	15.70 ± 17.7	0.001*	A e B
Animals	55.85 ± 30.06	51.09 ± 25.61	42.62 ± 29.8	0.24	
Cognitive Screening					
Int. HAD	10,61 ± 1.17	10.33 ± 1,49	9.74 ±1.76	0.07	
Motor Speed					
Gr – MD	41.02 ± 30.01	34.55 ± 29.53	20.35 ± 28.75)	0.045*	B
Gr- MND	39.11 ± 2 7.87	26.66 ± 23.74	14.40 ± 20.40	0.002*	B

(DP). p<0,05. RAVLT: The Rey Auditory-Verbal Learning Test; (IM: immediate, PI: post-interference, TR: late, RC: recognition); IHDS: International HIV Dementia Scale; Gr, Grooved Pegboard, MD: dominant hand; MND: non-dominant hand. F.A.S: Fuency VerbalA: No change x ANI; B: No change x MND; C: ANI x MDN.

DISCUSSION

We found a high prevalence of HAND (46.2%) in its two less severe forms, ANI (30.2%) and MND (16%), and only one case of dementia in our sample. These results confirm that a considerable number of patients continue to exhibit measurable cognitive dysfunction in the cART era in Brazil, where the potential availability of treatment is universal and free of charge (7). The overall frequency of HAND in our population was similar to that found in other studies, around 46% (ranging from 34 to 58%). However, another study using the same NP tests for 412 patients from other referral center found a 73.5% prevalence of HAND, being 50.9% ANI, 16.2% MND and 6.3% HAD (7). One possible reason for this difference may be related to the kind of population followed at each service. The better performance of our patients may be associated with their lower overall prevalence of morbidity: for instance, many were referred asymptomatic from blood banks to our service, and many of them never had any opportunistic infection. Similarly, a study found 84% prevalence of HAND among patients with previous self-perception of cognitive complaints (24% ANI, 52% MND, 8% HAD) and 64% among those who did not complain of difficulties in daily life (60% ANI) (43). The results of this study were similar to those obtained in other countries in Latin America (8-11).

There are few data on the prevalence of HAND in Brazil, their numbers ranging from 4.6% to 52.4% (5, 28-31). Such discrepancies, including the findings of this study, can be explained by different criteria used to define HAND, diversity of instruments used or size of the population studied. Also, the default of control variables may influence the results of neuropsychological tests, such as level of schooling, unemployment and depression. Regional features can also be important, as well as the type of co-morbidity and the prevalent HIV subtype. We tried to minimize these interferences during this study, using several forms to improve the quality of our database.

In this study, a higher prevalence of MND cases was observed in women. HIV-positive women may be at higher risk of cognitive decline than HIV-positive men, due to their high prevalence of psychosocial and mental health disturbances (32,33). Psychological suffering alone does not fully explain neurocognitive impairment among HIV-positive individuals. However, given the higher prevalence of depression among women compared to men, we speculate that the effects of depression on neuropsychological function are more widespread among HIV-positive women (34). We did not find a gender difference in mean viral loads values that could be associated with neurocognitive changes.

A study carried out in the United States found significant differences in cognitive function between men and women with HIV. Cognitive impairments are more prevalent in black women (52%), affecting mainly the area of memory. Low cognitive reserve, low reading level and unfavorable socioeconomic conditions were considered risk factors for cognitive impairment (35). Neuropsychological performance in a community sample of 237 PLWH compared to HIV-uninfected women was a significant predictor of slower psychomotor speed (36).

Neurocognitive performance testing in 149 HIV-positive women and 82 HIV-negative women enrolled in the Women's Interagency HIV Study (WIHS) demonstrated a psychomotor decline in PLWH when compared to healthy controls. In the intra-group analysis of women with HIV those not in use of antiretroviral therapy, compared to those undergoing treatment, had twice the risk of cognitive impairment, further supporting viremia as essential for HAND (37).

In this study, we found association of mood/affective symptoms with the outcome. Patients with late start of cART or recurrent depression may have significant cognitive and functional disturbances. On the other hand, these changes and symptoms may be due to a process of evolution of neurological-based cognitive impairment (38). However, a closer neuropsychological evaluation can trace the cognitive profile of those patients, helping with the differential diagnosis. In this study, all protocols were evaluated individually by an experienced neuropsychologist, avoiding false ANI and MND diagnosis.

Furthermore, it is important to emphasize that, other than HIV infection, no other cause seems likely to explain the presence of HAND, as patients with major depression, active drug dependence or opportunistic infection were excluded. Patients with the MND form also reported lower level of social and emotional support from their contact network, due to their seropositive condition. It seems advisable that, in addition to performing regular physical activity, a continuous stimulation of brain activities through social interactions and intellectual activities is encouraged to avoid cognitive dysfunction (6).

The cognitive profile of our patients without neurocognitive impairment was similar to those with ANI. There are controversies in the literature on both the definition, the significance and prognosis of patients with ANI. While some authors have shown that individuals with ANI may develop more severe forms of impairment, others have stressed that the definition of ANI is not strict and that the false positive rate is high (39, 40). However, regardless of the different opinions, HAND without functional consequences in daily life (asymptomatic neurocognitive impairment) is still the most frequent form (2, 9). The current classification of HAND by Frascati's criteria, particularly of the ANI form, may overestimate the prevalence of this condition, since the definition of ANI is not strict and its application results in approximately 20% of the population being classified as abnormal, that is, false-positives, what is an unacceptable rate (40).

Our study has some limitations, such as its sample size (24.6% of the cohort). We intend to perform neuroimaging in the future, what may further enhance the precision of our findings. Despite those limitations, we sought to control for confounding factors, such as age, gender and education, as well as for confounders for the diagnosis of HAND, such

as major depression and co-infection. Another limitation of the study is lack of control group, but Brazilian normative tables were used in the correction of the instruments used in this study (24-26).

On this study, we employed a complex neuropsychological assessment compared to other studies. In addition to the cognitive screening test (IHDS), we used neuropsychological instruments that enable a better understanding of the higher cognitive functions, allowing a greater precision in the detection of cognitive impairment. Usually, the studies have used a screening battery made up of three or four neuropsychological instruments (28-31).By contrast, in the present study, seven neuropsychological instruments were used, in addition to the IHDS, increasing the rigor of the rating. Our patients have a high degree of adherence to cART, with over 95% adherence and viral load detection (17). Such characteristics make this cohort somewhat specific compared to other Brazilian cohorts. Finally, we found a high prevalence of HAND (46.2%), mainly among women. A longitudinal follow-up to of such patients is very important, in order to address the incidence and additional risk factors associated with HAND in Brazil, particularly concerning the gender differences we found.

Acknowledgements: We thank Dr. David M. Margolis in UNC HIV Cure Center for his insightful comments. We dedicate this work for all patients along 30 years and ex-medical residents whom cared for them. We also thank the volunteers Maria Olímpia Ribeiro Freitas and Maria Tereza de Figueiredo for volunteering for more than 20 years at the ADEEE3002, HIV outpatient clinic, Hospital das Clínicas da FMUSP.

REFERENCES

1.Centers for disease control and prevention. HIV Surveillance Report. [Online]: 2018. [Cited 2019 November. Available from: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2018-preliminary-vol-30.pdf. Accessed 10 January 2020.

2.UNAIDS. Global Aids Update. [Online]. 2019 [Available from: https://www.unaids.org/en/resources/documents/2019/2019-global-AIDS-update. Accessed 10 January 2020.

3.Nightingale S, Winston A, Letender S, Michael RD, McArthur JC, Khoo S, Solomon T. Controversies in HIV-associated neurocognitive disorders. Lancet Neurol. 2014 13(11):1139-51. doi: 10.1016/S1474-4422(14)70137-1. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4313542/

4.Troncoso FT, Conterno Leo. Prevalence of neurocognitive disorders and depression in a Brazilian HIV population. Rev Soc Bras Med Trop. 2015 48(4):390-398.

5.Chan P, Brew BJ. HIV associated neurocognitive disorders in the modern antiviral treatment era: prevalence, characteristics, biomarkers, and effects of treatment. Curr HIV/AIDS Rep. 2014 11(3):317-324.

6.Sheppard DP, Woods SP, Doyle KL, Verduzco. Random Number Generation in HIV Disease: Associations with Neuropsychological Functions and Activities of Daily Living. Arch Clin Neuropsychol. 2017;32(1):53-62.

7.Gascón MRP, Vidal JE, Mazzaro JS, Marcusso RMN, Capitão CG, Coutinho EM, Benute GRG, Lucia MCS, Oliveira ACP. Neuropsychological assessment of 412 HIV-infected individuals in São Paulo, Brazil. AIDS Patient Care STDS. 2018 32:1-8.

8.Martínez-Banfi M, Vélez JI, Perea MV, García R, Puentes-Rozo PJ, Mebarak Chams M, Ladera V. Neuropsychological performance in patients with asymptomatic HIV-1 infection. AIDS Care. 2018;30(5):623-633.

9.Sartori GP, Domínguez CI, Rodríguez VG, Dansilio S, Presenteado JCM. Transtornos neurocognitivos en pacientes VIH positivos. Datos preliminares de una cohorte prospectiva uruguaya. Rev. Med Urug.2019; 35 (3): 171-180.

10.Miozzi G. Relación entre transtornos neurocognitivos con el uso de terapia antirretrovrial en pacientes que viven con virus de imunodeficiencia humana atendidos en la consulta de infectología, ciudad hospitalaria " Dr Enrique Tejera" Valencia, Venezuela, enro-agosto, 2014. Universidad de Carabobo, Faculdad de Ciencias de la Salud, Dirección de Postgrado - Titulo de Especialista en Infectología.Available from: https://pesquisa.bvsalud.org/portal/resource/pt/biblio-1024096

11. Heikinheimo T, Poutiainen E, Salonen O, Elovaara I, Ristola M. Three-decade neurological and neurocognitive follow-up of HIV-1-infected patients on best-available antiretroviral therapy in Finland. BMJ Open. 2015 Nov 5;5(11):e007986.

12.Brew BJ, Chan P. Update on HIV dementia and HIV-associated neurocognitive disorders. Curr Neurol Neurosci Rep. 2014 14(8):468.

13.McArthur JC, Steiner J, Sacktor N, Nath A. Human immunodeficiency virus-associated neurocognitive disorders: Mind the gap. Ann Neurol. 2010 67(6):699-714.

14.Tsegaw M, Andargie G, Alem G, Tareke M. Screening HIV-associated neurocognitive disorders (HAND) among HIV positive patients attending antiretroviral therapy in South Wollo, Ethiopia. J Psychiatr Res. 2017 85:37-41.

15.Ian E, Gwen CL, Soo CT, Mellissa C, et al. The burden of HIV-associated neurocognitive disorder (HAND) in the Asia-Pacific region and recommendations for screening. Asian J Psychiatr 2016 22:182-189.

16.Thaler NS, Sayegh P, Arentoft A, Thames AD, Castellon SA, Hinkin CH. Increased neurocognitive intra-individual variability is associated with declines in medication adherence in HIV-infected adults. Neuropsychology. 2015;29(6):919-25.

17.Casseb J, Fonseca LAM, Duarte A. Is it possible to control HIV infection in a middle-income country through a multidisciplinary approach? AIDS Res Hum Retroviruses. 2018;34(2):165-167.

18.Sacktor NC, Wong M, Nakasujja N,Skolasky RL, Selnes OA, Musisi S, Robertson K, McArthur JC, Ronald A, Katabira E. The International HIV Dementia Scale: a new rapid screening test for HIV dementia. AIDS. 2005 19(13):1367-1374.

19.Santos R L, Junior JSV. Confiabilidade da versão Brasileira da Escala de Atividades Instrumentais da Vida Diária. Brazilian Journal in Health Promotion. 2008 21(4):290-296.

20.Botega NJ, Bio MR, Zomignani MA, Garcia Jr C, Pereira WAB. Transtornos do humor em enfermaria de clínica médica e validação de escala de medida (HAD) de ansiedade e depressão. Revista de Saúde Pública. 1995;29:359-63.

21.Henrique IFS, de Micheli D, de Lacerda RB, de Lacerda LA, Formigoni MLOS. Validação da versão brasileira do teste de triagem do envolvimento com álcool, cigarro e outras substâncias (ASSIST). Revista da Associação Médica Brasileira. 2004 50:199-206.

22.Seidl EMF, Tróccoli BT. Desenvolvimento de escala para avaliação do suporte social em HIV/aids. Psicologia: Teoria e Pesquisa. 2006 22:317-326.

23.Remor E, Milner-Moskovics J, Preussler G. Adaptação

brasileira do "Cuestionario para la Evaluación de la Adhesión al Tratamiento Antiretroviral". Revista de Saúde Pública. 2007 41:685-694.
24. Weschsler D. WAIS III- Escala de inteligência para adultos: manual: Casa do Psicólogo, 2004.
25. Malloy-Diniz LF, Lasmar VAD, Gazinelli LSR, Fuentes D, Salgado JV. The Rey Auditory-Verbal Learning Test: applicability for the Brazilian elderly population. Rev Bras Psiquiatr. 2007 29(4):324-329.
26.Strauss E, Sherman E, Spreen O. A compendium of neuropsychological tests: Administration, norms, and commentary. 3 ed. New York: Oxford University Press, 2006.
27.Casseb J, Fonseca LA, Veiga AP, de Almeida A, Bueno A, Ferez AC, Gonsalez CR, Brigido LF, Mendonça M, Rodrigues R, Santos N, Malacarne E, Ronchini KO, Zihlmann KF, Duarte AJ. AIDS incidence and mortality in a hospital-based cohort of HIV-1-seropositive patients receiving highly active antiretroviral therapy in São Paulo, Brazil. AIDS Patient Care STDS. 2003;17(9):447-452.
28.Pinheiro CAT. Alterações neurocognitivas por comprometimento subcortical em pacientes com HIV / AIDS em uma região do sul do Brasil [Dissertação] Universidade Católica de Pelotas, 2016. Available from: http://tede.ucpel.edu.br:8080/tede/handle/tede/512.
29.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(10):1648-1655.
30.Kalil RS, Alvarenga RMP, Almeida AJd, Morais-de-Sá CA. Estudo dos transtornos cognitivos decorrentes da infecção pelo HIV-1. Estudos de Psicologia (Campinas). 2009; 26:465-473.
31.Oliveira JF, Greco DB, Oliveira GC, Christo PP, Guimarães MDC, Oliveira RC. Neurological disease in HIV-infected patients in the era of highly active antiretroviral treatment: a Brazilian experience. Rev Soc Bras Med Trop. 2006;39(2):146-151.
32.Rubin LH, Neigh GN, Sundermann EE, Xu Y, Scully EP, Maki PM. Sex Differences in Neurocognitive Function in Adults with HIV: Patterns, Predictors, and Mechanisms. Curr Psychiatry Rep. 2019;21(10):94.
33.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(9):1243-1250.
34.Pauline M. Maki; Eileen Martin-Thormeyer. HIV, Cognition and Women Neuropsychol Rev. 2009 Jun; 19(2): 204–214.
35.Sundermann, Erin E.; Heaton, Robert K.; Pasipanodya, Elizabeth Moore, Raeanne C. Paolillo, Emily W. Rubin, Leah H.Ellis, Ronald; Moore, David J.the HNRP GrouP. Sex differences in HIV-associated cognitive impairment. AIDS. 2018;32(18):2719-2726.
36.Durvasula RS, Miller EN, Myers HF, Wyatt GE. Predictors of neuropsychological performance in HIV positive women. Journal of Clinical and Experimental Neuropsychology. 2001 23(2):149–163.
37.Richardson JL, Martin EM, Jimenez N, Danley K, Cohen M, Carson VL, et al. Neuropsychological functioning in a cohort of HIV infected women: importance of antiretroviral therapy. Journal of the International Neuropsychological Society. 2002 8(6):781–793.
38.Cysique LA, Dermody N, Carr A, Brew BJ, Teesson M. The role of depression chronicity and recurrence on neurocognitive dysfunctions in HIV-infected adults. J Neurovirol. 2016 22(1):56-65.
39.Grant I, Franklin DR, Deutsch R, Woods SP, Vaida F, Ellis RJ, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurology. 2014;82(23):2055-2062.
40.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.