Original Article

Normative Scores for Select Neuropsychological Battery Tests for the Detection of HIV-Associated Neurocognitive Disorder amongst Nigerians

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Abstract

Background: The study aimed to derive socio-demographic–corrected norms for selecting neuropsychological (NP) battery tests for people living with HIV (PLWHIV) in Nigeria. This cross-sectional study was conducted amongst patients who attended the general outpatient clinic and junior staff of the University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla. **Aims and Objectives:** To determine the normative scores for select neuropsychological battery test for the detection of neurocognitive disorder amongst Nigerians PLWHIV. A sample of 92 individuals received voluntary HIV testing. **Methods:** Eligibility criteria were being HIV negative, aged 18–64 years and formal education. We undertook a brief neuromedical examination to identify putative exclusion criteria. We sampled four NP tests covering seven cognitive domains and the motor speed component of the International HIV Dementia Scale (IHDS-MS). We presented the normative scores using statistics of mean, median, standard deviation (SD), kurtosis and skewness. **Results:** All the participants were Nigerians aged 18–64 years. Most (74.1%) of the participants were females. The mean and median ages of the participants were 42.6 ± 11.42 years and 44 years, respectively. The effect of gender on NP performance was limited to the digit span test (DST)-forwards, while education affected all expect IHDS-MS and DST-backwards. The cut-off scores for defining mild and severe impairment varied (moving from 1SD to 2SD) for all cognitive domains except for IHDS-MS and DST. **Conclusions:** With these preliminary normative scores, it will be easier to identify and classify the severity of neurocognitive impairment amongst PLWHIV in Nigeria, thus facilitating the goal of keeping HIV-associated dementia to a minimum. The lack of variability in the IHDS-MS and DST is unfavourable.

Keywords: Diagnosis, HIV, neurocognitive disorder, Nigeria, normative score

Introduction

Despite the rising prevalence of HIV-associated neurocognitive disorder (HAND), diagnosing HAND is difficult,[1,2] particularly in resource-strapped sub-Saharan Africa, where over half of HIV patients live.[3] Cultural diversity makes generalisability problematic when it comes to HAND diagnosis.[4] Numerous short measures include the popular International HIV Dementia Scale (IHDS). However, their utility is typically restricted by substantial variations in sensitivity and specificity.[5] The neuropsychological (NP) battery measures are the standard of excellence in the diagnosis of HAND.[6,7] Notwithstanding, NP tests are rife with demographics and cultural bias, making them ineffective in a variety of clinical settings.[1] Following the widespread use of anti-retroviral medication, the prevalence of HIV-associated dementia (HAD) has dropped dramatically, yet mild but limiting forms of HAND have continued to rise.[8] There is a pressing need to accurately identify HAND, especially in resource-constrained sub-Saharan Africa.[5]

Several screening measures have been used to diagnose HAND, including HIV dementia scale,[9] mental alternation tests,[10] IHDS[11] and EXIT interview.[12] However, due to their

Received: 05-02-2022, **Revised:** 04-05-2022,
Accepted: 17-05-2022, **Published:** 22-07-2022

Access this article online

Quick Response Code:

Website: www.npmj.org

DOI: 10.4103/npmj.npmj_31_22

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How to cite this article: Nweke M, Mshunqane N, Govender N, Akinpelu AO, Ogunniyi A. Normative scores for select neuropsychological battery tests for the detection of HIV-associated neurocognitive disorder amongst Nigerians. Niger Postgrad Med J 2022;29:262-7.

failure to detect mild forms of HAND, their clinical utility is limited.[13] Failure to diagnose the moderate and sub-clinical forms of HAND could result in mild impairment becoming severe impairment.[14] The disadvantages of using gold standard NP test batteries include their inconvenient nature and the fact that they are prone to culture variation,[1] yet their merit lies in the capacity to detect sub-clinical forms of HAND.[5] For example, deficit-defining cut-off scores for the Trail Making Test (TMT) differ with settings which if ignored could lead to a major diagnostic error.[1] Surprisingly, there are few published normative scores for the NP test in sub-Saharan Africa despite serving as home to more than half of all people living with HIV (PLWHIV). In sub-Saharan Africa, the only published adult norms for NP battery tests[5] were carried out amongst South Africans and covered four relevant cognitive domains. At present, Nigeria possesses a high burden of HIV being the second only to South Africa where 3.2 million PLWHIV live.[15,16] The aim of our study was to produce a preliminary reference scores for selected NP tests that can be used in Nigerian setting to examine neurocognitive ability domains that are typically impaired by HIV infection.

Materials and Methods

Design and research setting

We conducted a cross-sectional study involving patients who attended the general outpatient clinic and junior staff of the University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla. The UNTH is a federal government-owned tertiary health facility and the pioneer teaching hospital located at Enugu, Nigeria. The hospital is the main referral facility providing both adult and paediatric HIV care for South-eastern Nigeria. The study started in September 2020 and was completed in October 2020. A sample of 92 individuals received voluntary testing. The HIV testing was provided at no cost and in a confidential manner to all eligible subjects. The study was approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria, South Africa (protocol number: 152/2020). The study was approved on 15th June 2020.

Study participants

Participants constituted HIV-negative patients who attended the general outpatient clinic and staff (cleaners, security officers and record officers) of the UNTH. Participants were recruited using convenient sampling. To limit bias, we ensured that selected participants possessed similar socio-demographic characteristics as do the HIV-positive patients in our setting. The eligibility criteria were being HIV-positive or HIV-negative, aged 18–64 years and ability to understand and use English. The exclusion criteria were, inability to use English, history of major cardiovascular disease or risk factors, e.g., uncontrolled hypertension (blood pressure [BP] 140/90 mmHg), history of seizure disorder, stroke, head injury with loss of consciousness >30 min, psychotic disorders, active major depression, substance abuse and alcoholism, acute illness, leading to a reduction in activities of daily living (ADL), pregnancy, deafness and partial blindness. Of the 92 individuals who underwent HIV screening, a total of 82 participants met the eligibility criteria and were subjected to further NP testing. Before enrolment, we obtained informed consent.

Materials

Depression will be assessed using the Beck Depression Inventory (BDI), which is a 21-item self-report instrument that measures characteristics, attitudes and symptoms of depression. It possesses internal consistency of 0.73–0.92.[17] The BDI possesses high internal consistency (Cronbach's alpha: 0.86 and 0.81) for both psychiatric and non-psychiatric populations.[18] A score of 17 is indicative of borderline clinical depression.[19] It takes about 10 min to administer.[17] We assessed alcohol intoxication using the Alcohol Use Identification Test (AUDIT). The AUDIT is a valid brief instrument for the assessment of intoxication and withdrawal. It is a ten-item questionnaire that is valid and reliable, and a score of 8 indicates alcohol intoxication or withdrawal and justifies exclusion.[20] Individuals who score 8 and above are said to have alcohol intoxication, which warrants exclusion.[20] It is completed within 2–4 min. The drug abuse and substance test is a ten-item questionnaire that is valid and reliable, and a score of 3 indicates drug abuse, which warrants exclusion.[20,21] It takes about 5 min to be completed. Motor skill was assessed using the first item of the IHDS owing to the unavailability of the grooved pegboard test. Notwithstanding, the IHDS is a valid measure of probable dementia amongst PLWHIV.[11]

We assessed verbal learning (VL) and memory using the Hopkins Verbal Learning Test–Revised (HVLT-R). It is simple to administer and possesses a high correlation with the California VL Test.[22] In the HVLT-R, 12 words with an embedded semantic structure (four categories of three words each) were listed and given to the participants who were asked to repeat as many words as they could remember in any order after the examiner read the list to them (free recall). Three times the trial was held, followed by a delayed recall period of 25 min. The sum of the three trials constituted the HVLT-R VL score, while the number of recalled after 20–25 min constituted the HVLT-R delay recall (DR). Form 6 of the HVLT-R was used; previous studies have demonstrated the equivalence of form.[23] We assessed information processing speed and executive function using the TMT. The TMT is a valid and simple paper-and-pencil test that assesses executive function/abstraction and speed of information processing and possess two parts.[24] The TMT-A is a page with encircled numbers 1–25. We asked the patients to connect the numbers in the correct pattern quickly on the TMT-A. In the same vein, on the TMT-B, numbers 1 through 13 as well as the letters A through L are scattered. We instructed participants to draw lines in the proper order, with numbers and letters alternated. Correctness and time of completion of each part were recorded.

We assessed attention and working memory using the digit span test (DST). The DST is a paper-and-pencil test that assesses attention and working memory derived from oral information.[25] Working memory and attention were assessed using the DST. It was created for people ranging in age from 18 to 97 years, making it a good fit for this study. Series of digits were repeated by the participants. The highest digit span that an individual could repeat in direct order formed the DST-forwards (DST-f) score, while the highest digit span that an individual could repeat in reverse order determined the DST-backwards (DST-b) scores.[25,26] The Controlled Oral Word Association Test (COWAT) is a reliable test that assesses a person's ability to locate specific information within predetermined search parameters.[27,28] We required individuals to name as many words as they could that began with a letter, such as F, A and S. Each letter had a time limit of 60 s. We restricted participants from using name and numbers. Scoring was based on the total number of words retrieved within 3 min.

Data collection procedures

Before NP, we conducted a brief neuromedical examination to identify eligible participants. Preliminary data sought socio-demographic characteristics, depression, alcohol use, substance abuse, history of the cardiorespiratory disease, focal neurological deficit, stroke, traumatic brain injury with a history of loss of consciousness, psychiatric illness, BP greater than 140/90 mmHg and acute illness limiting ADL. According to the Frascati criteria, NP evaluation for PLWHIV should cover at least five ability domains commonly impaired amongst PLWHIV, including executive function, VL, memory, information processing speed, working memory, attention and verbal fluency.[6] Four NP tests, namely the HVLT-R, TMT, DST and COWAT-FAS covering seven ability domains, were used in this study.

Data analysis

Data gathered were collated, cleansed and analysed using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp., Armonk, New York, USA). Descriptive statistics of frequencies, percentages, means and standard deviations (SDs) were used to present data on socio-demographic characteristics. To establish which socio-demographic variables may constitute bias, thus requiring demographic correction, we fitted multiple regression models. In the model, level of education, gender and age acted as the explanatory variables. There was no significant correlation between age and any of the NP test variables. Sex was correlated with DST-f. Table 1 shows that education correlated with HVLT-R learning, HVLT-R DR, TMT-A, TMT-B, DST-f and COWAT. Hence, we stratified the NP test performance according to gender and education based on the findings in Table 1. For age stratification, given the mean, we grouped the participants into two categories, namely 44 years and >44 years. We presented normative scores with the aid of descriptive statistics of mean, median, SD, skewness and kurtosis. To improve the clinical usefulness of the data, we present 1SD and 2SD of the NP test as integers. According to the Frascati criteria,[6] a performance deficit up to 1SD or 2SD is indicative of impairment in a given cognitive domain.

Table 1: Linear multiple regression displaying the influence of age, gender and education categories on neuropsychological tests scores

	IHDS MS		HVLT-R learning		HVLT-R DR		TMT-A		TMT-B		DST-f		DST-b		COWAT	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Age	0.094	0.452	−0.112	0.349	−0.189	0.103	0.215	0.062	0.094	0.361	−0.111	0.300	−0.026	0.831	−0.004	0.970
Sex	−0.160	0.531	−0.012	0.914	0.011	0.914	−0.006	0.955	0.066	0.483	−0.245	0.013*	−0.141	0.204	−0.165	0.088
Education	−0.078	−0.291	0.277	0.022*	0.310	0.008*	−0.295	0.011*	−0.540	<0.001*	0.399	<0.001*	0.238	0.054	0.513	<0.001*

*Significant at $P<0.05$. IHDS MS: Motor skill component of the International HIV Dementia Scale, HVLT-R learning: Learning component of the Hopkins Verbal Learning Test-Revised, HVLT-R DR: Delayed recall component of the Hopkins Verbal Learning Test-Revised, TMT-A: Trail Making Test-A, TMT-B: Trail Making Test-B, DST-f: Digit span test-forwards, DST-b: Digit span test-backwards, COWAT: Controlled Oral Association Test, β: Odds ratio

Results

In this study, all the participants were Nigerians aged 18–64 years. Most (74.1%) of the participants were females. The mean and median ages of the participants were 42.6 ± 11.42 years and 44 years, respectively. The number of participants who attained secondary and tertiary education was 35 (42.7%) and 33 (40.2%), respectively. Gender and education had a significant impact on NP test performance. Specifically, the effects of gender were limited to DST-f performance ($P = 0.013$), while education affected all expect IHDS-motor speed (IHDS-MS, $P = -0.291$) and DST-b ($P = 0.054$) [Table 1]. Men with tertiary education possessed a higher DST-f deficit cut-off score compared to their female counterparts. The effects of education on HVLT-R learning, HVLT-R DR, TMT-A, TMT-B, DST-f and COWAT are uniform, with tertiary education recording the highest deficit cut-off scores. The cut-off scores for defining mild and severe impairment varied (moving from 1SD to 2SD) for all cognitive domains, except for IHDS-MS (for both men with primary and secondary education), DST-f (amongst women with primary education) and DST-b (amongst men with primary education and women with secondary education) [Table 2].

Discussion

Despite the growing need to diagnose and treat HAND amongst Nigerians living with HIV, this study is the first to provide locally relevant norms for PLWHIV in Nigeria. These assessments, interestingly, cover cognitive regions that are typically impaired by HIV infection. As a result, the normative scores reported providing clinicians and researchers with a basis for identifying and classifying HAND using the Frascati criteria.[6] Given the findings, it will be easier to identify and classify the severity of neurocognitive impairment amongst PLWHIV in Nigeria, making it easier to achieve the goal of keeping HAD to a minimum. Furthermore, stratifying data by gender and educational level will improve the study's utility.[5] We discovered that gender has an impact on neurocognitive performance, particularly digit span forward (DST-f), in this study (attention). This supports the use of socio-demographic–corrected normative scores for the DST-f in the country and highlights the study's strength. The normative scores for the DST-f, digit span backward (DST-b) and the Colour Trails text were produced in Uganda by Robertson *et al*.[7] However, neglecting the effect of gender on DST-f could compromise the diagnostic method's accuracy. Our findings support those of Singh *et al*.,[5] who studied HIV-positive South Africans. Age was linked to DSB performance, according to Singh *et al*.[5] In contrast to Singh *et al*., we found no significant gender effect on DST-b. The discrepancy may be due to Singh *et al*.'s failure to treat DST-f and DST-b as distinct cognitive domains.

Interestingly, amongst this Nigeria HIV population, education was the most important factor that affected neurocognitive performance, specifically HVLT-R learning, HVLTR DR, TMT-A, TMT-B, DST-f and COWAT. Education has a consistent effect; individuals with a tertiary education possess the highest deficit cut-off scores, followed by those with secondary education. This is in line with the findings of Mitrushina *et al*.[29] and Tombaugh[30] amongst Caucasians, but it contradicts Singh *et al*., who found no link between education and neurocognitive performance amongst HIV-positive South Africans. Our sample's median educational attainment, like Singh *et al*.,[5] is secondary, with an estimated 10–12 years of education. Our sample size is similar to Singh *et al*.;[5] however, unlike Singh *et al*., the degree of education correctly represents educational inequalities amongst PLWHIV in Nigeria. Notably, age differences did not pose a significant threat to NP performance in our population when educational attainments were equal (for the HVLT-R learning, HVLT-R DR, TMT-A, TMT-B and COWAT) and educational attainment and gender were equal (for the DST-f).

Overall, our findings support the call for culture-specific NP test standards in the PLWHIV population. The use of cross-cultural data for an NP test, according to Fernández and Marcopulos,[1] will result in errors in HAND classification. For example, Singh *et al*.[5] found that female participants took an average of 40.71 s and 72.57 s to complete the TMT-A and TMT-B, which did not vary with education. In our sample, however, the average time to complete the TMT-A and TMT-B was 61.75 and 151.88 for primary school leavers, 55.88 and 141 for secondary school graduates and 36.14 and 87.62 for those with tertiary education. The lack of variability in women's IHDS-MS, DST-f and DST-b performance, as well as men's IHDS-MS and DST-b performance, may limit the DST test's clinical utility amongst PLWHIV in Nigeria. Because 2 is the deficit cut-off for both mild (1SD) and severe (2SD) impairments, it will be difficult to classify the degree of impairment if a man with primary education repeats 2 digits on the DST-b. As a result, we recommend Automated Working Memory Assessment as an alternative to the DST-b for assessing working memory in PLWHIV in Nigeria. Similarly, for motor skill evaluation, we recommend the grooved pegboard.

The small sample size utilised in this preliminary study constitutes a limitation. Although true population norms normally require a minimum sample of close to 1000 participants, the cost implications make it often unfeasible, especially in the face of limited research funding. Similar challenges have been encountered by authors who have reported normative scores for selected NP tests.[5,9,31] Although the outcome of our study may not apply to all PLWHIV in Nigeria, the country's lack of NP reference data, combined with the need to detect, categorise and treat HAND, makes it all the more important. In conclusion, the use of cross-cultural NP test norms could lead to an incorrect classification of HAND. The lack of variety in the IHDS-MS item, as well as DST-f and DST-b, is unfavourable. One of our study's strengths is the presentation of detailed normative statistics and socio-demographic–stratified norms.

Table 2: Normative scores for International HIV Dementia Scale motor speed item, learning component of the Hopkins Verbal Learning Test-Revised, delayed recall component of the Hopkins Verbal Learning Test-Revised, Trail Making Test-A, Trail Making Test-B, digit span test-forwards, digit span test-backwards and Controlled Oral Association Test

Sex	Mean (SD)	Median	Minimum-maximum	Skewness	Kurtosis	1SD from $\bar{X}$	2SD from $\bar{X}$
Male (*n*=21)							
Primary							
Motor speed	3.83 (0.41)	4	3-4	−2.45	6.00	3	3
HVLT-R learning	19.33 (3.56)	18.5	16-26	1.63	3.05	16	12
HVLT-R DR	5.80 (2.28)	6	2-8	−1.49	2.82	4	1
TMT-A	61.67 (33.77)	45.5	36-124	1.65	2.31	95	129
TMT-B	173.8 (13.86)	180	149-180	−2.24	5.00	188	202
DST-f	4.83 (1.47)	4.5	3-7	0.42	−0.86	3	2
DST-b	3.1 (0.75)	3	2-4	−0.31	−0.10	2	2
COWAT	23.67 (8.89)	23	10-34	−0.41	−0.48	15	6
Secondary							
IHDS MS	3.67 (0.58)	4	3-4	−1.73	-	3	3
HVLT-R Learning	21.00 (3.61)	20	18-25	1.15	-	17	14
HVLT-R DR	5.67 (0.58)	6	5-6	−1.73	-	5	4
TMT-A	48.33 (3.51)	48	45-52	0.42	-	52	55
TMT-B	103.3 (37.81)	90	74-146	1.39	-	141	179
DST-f	4.33 (0.58)	4	4-5	1.73	-	4	3
DST-b	3.33 (0.58)	3	3-4	1.73	-	3	2
COWAT	33.67 (4.93)	36	28-37	−0.65	-	29	24
Tertiary							
IHDS MS	3.64 (0.67)	4	2-4	−1.80	0.66	3	2
HVLT-R Learning	22.33 (2.53)	23.5	19-25	−0.37	−1.83	20	17
HVLT-R DR	7.33 (1.87)	8	2-9	−2.37	6.54	5	4
TMT-A	42.64 (19.41)	34	28-93	2.12	0.66	62	81
TMT-B	87.18 (27.93)	92	34-114	−0.76	0.66	115	143
DST-f	5.67 (0.78)	5.5	5-7	0.72	−0.79	5	4
DST-b	3.67 (0.79)	3.5	3-5	0.72	−0.79	3	2
COWAT	36.00 (7.87)	35	27-49	0.40	1.23	28	20
Female (*n*=60)							
Primary							
IHDS MS	3.5 (0.53)	3.5	3-4	0.00	−2.80	3	2
HVLT-R Learning	19.25 (3.81)	19	12-24	−0.59	1.27	15	12
HVLT-R DR	4.00 (1.77)	6	1-6	−0.62	−0.39	2	0
TMT-A	61.75 (22.51)	60	32-91	0.08	−1.69	84	107
TMT-B	151.88 (37.0)	172	90-180	−0.95	−0.87	189	226
DST-f	4.00 (0.53)	4	3-5	0.000	3.5	3	3
DST-b	3.00 (0.76)	3	2-4	0.000	−0.70	2	1
COWAT	18.63 (7.46)		12-35	1.80	3.42	11	4
Secondary							
IHDS MS	3.58 (0.56)	4	2-4	−0.93	−0.08	3	2
HVLT-R Learning	20.16 (4.38)	21	13-28	0.05	−1.11	16	11
HVLT-R DR	6.47 (2.66)	7.5	3-11	0.37	−1.37	4	1
TMT-A	55.88 (26.48)	48.5	21-129	1.03	0.75	82	109
TMT-B	141.19 (41.66)	153	56-180	−0.62	−0.69	183	225
DST-f	4.40 (0.76)	4	3-6	0.10	−0.13	4	3
DST-b	3.00 (0.72)	3	2-5	0.56	0.80	2	2
COWAT	23.56 (8.46)		8-41	0.24	−0.20	15	7
Tertiary							
IHDS MS	3.43 (0.51)	3	3-4	0.31	−2.12	3	2
HVLT-R Learning	22.70 (4.38)	22	15-31	0.20	−0.55	18	14
HVLT-R DR	7.4 (2.1)	2	4-11	−0.07	−1.14	5	3
TMT-A	36.14 (11.41)	34	20-58	0.61	−0.50	48	59

Contd...

Table 2: Contd...

Sex	Mean (SD)	Median	Minimum-maximum	Skewness	Kurtosis	1SD from $\bar{X}$	2SD from $\bar{X}$
TMT-B	87.62 (42.14)	80	20-180	0.61	−0.04	130	172
DST-f	5.24 (0.83)	5	4-7	0.08	−0.47	4	4
DST-b	3.55 (1.10)	3	2-7	1.58	5.32	2	1
COWAT	36.38 (13.12)		12-75	0.78	3.10	23	10

IHDS MS: Motor skill component of the International HIV Dementia Scale, HVLT-R learning: Learning component of the Hopkins Verbal Learning Test-Revised, HVLT-R DR: Delayed recall component of the Hopkins Verbal Learning Test-Revised, TMT-A: Trail Making Test-A, TMT-B: Trail MAKING TEST-B, DST-f: Digit span test-forwards, DST-b: Digit span test-backwards, COWAT: Controlled Oral Association Test, $\bar{X}$: Mean, SD: Standard deviation

Conclusion

The findings of the study can be used to standardise NP examinations in Nigerian languages. The study's majority of participants were females, which is desired because women endure a bigger burden of HIV chronicity than men.[5] Following Mitrushina *et al.*,[29] we presented a detailed description of the inclusion and exclusion criteria, gender distribution, sample size and the descriptive statistics of the NP data were all thoroughly described.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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