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Diagnostic Utility of the International HIV Dementia Scale for HIV-Associated Neurocognitive Impairment and Disorder in South Africa

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Abstract

Studies in sub-Saharan Africa indicate that most HIV seropositive persons suffer from HIV-associated neurocognitive disorder (HAND). HAND diagnosis is facilitated by specific screening. Seventy participants were recruited from an HIV voluntary counseling and testing clinic in Durban, South Africa. The diagnostic utility of the International HIV Dementia Scale (IHDS) was analyzed employing a Receiver Operating Characteristic (ROC) model. The ROC analysis comparing any HAND diagnosis (based on two neuropsychological tests) versus no diagnosis was statistically significant, with an optimal cut-off score of 10.5, sensitivity 69%, and specificity 74%. Sensitivity of the IHDS was highest for HIV-associated dementia.

HIV-associated neurocognitive impairment (NCI) and disorder occurs in 25–60% of HIV infected patients internationally {1}. Overall, studies from North America and Western Europe have focused upon the most severe form of HIV-associated neurocognitive disorder (HAND) – HIV-associated dementia (HAD) {2}. However, the cumulative risk for this disorder now is estimated to be only 2% of HIV-infected persons in the USA {3}. A milder form of HAND, mild neurocognitive disorder (MND), is estimated at a prevalence of 12%. MND, in turn, is bordered by the less severe, sub-clinical condition of HIV-associated asymptomatic neurocognitive impairment (ANI) -- currently estimated at a prevalence of 33%. With the reduced prevalence of HAD, MND has become a more important focus for clinical intervention – analogous to minor cognitive impairment versus Alzheimer's Disease in the general population. Reports from sub-Saharan Africa {4–8} suggest that a variety of factors may cause a divergence from HAND rates observed in North America and Western

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Europe, including a greater divergence in HIV clades (particularly a higher frequency of clade C), a greater frequency as well as divergence of HIV-associated and CNS-specific comorbidities, more patients at an advanced HIV disease stage, and lower access to effective antiretroviral therapy (ART). In kind, HAND may be similarly improved by current antiretroviral (ARV) regimens {8}. Despite the established benefit of making HAND diagnoses worldwide, the process of establishing the reliability and validity of HAND diagnoses in sub-Saharan Africa remains challenging.

The diagnosis of HAND by the Frascati conference criteria {9} prioritizes the administration of a neuropsychological (NP) test battery. This is not feasible in VCT testing clinics in South Africa because it requires a neuropsychologist, a trained psychometrist, specialized NP testing materials, and as much as 2–3 hours of assessment time per patient. Screening tests for HAND have been recommended by the Frascati conference {9} in such limited-resource settings, and several screening tests for HAND have been utilized {10–13}. Ganasen et al. reported that one of these screening tests, the HIV Dementia Scale (HDS), showed a sensitivity and specificity of approximately 80% in a South African sample {14}. However, this may well represent an over-estimate because the comparator was another screening test more sensitive to cortical dysfunction - the Mini-Mental Status Examination – as opposed to a comprehensive, HIV-specific NP test battery focused more upon subcortical dysfunction. The HDS has been widely studied as a screening test for HAND in numerous HIV infected samples {cf. 15–18}. One issue has been the scoring of the anti-saccadic eye movement error item {18}. In addition, the timed alphabet and cube copy items are susceptible to cultural bias. Hence, the International HIV Dementia Scale (IHDS) was developed to address this issue of cultural bias. It is a brief, culturally neutral test not requiring English language knowledge, high educational level, or special instrumentation and can be administered by trained, non-clinical personnel {11}.

The use of the IHDS has been supported by several studies. Per the South African ARV roll-out program, patients with AIDS-defining illnesses, including HAD {19,20}, are eligible for ARVs -- regardless of CD4 cell count. The study's aim was to determine the potential utility of the IHDS in an ARV-naïve sample expected to benefit from HAND screening. At the time of this study, patients with CD4 cell count < 200 cells/mm³ were considered treatment-eligible in South Africa. Hence, we chose a CD4 cell count range that was next higher (200–350 cells/mm³) to administer the IHDS as a HAND screening test (together with a brief NP test assessment for HAND) in an ARV-naïve sample. The IHDS had been initially standardized against a larger NP battery as well as neurological examination and a functional status assessment. The association of the IHDS with NP test performance was consistent across NP tests in that study. Thus, we anticipated that this would justify our selection of a smaller NP battery from that group of tests. We focused upon two tests given there – Digit Span and the Trail Making Test, both of which showed significant associations with the IHDS score in a similar population, the Ugandan population. Moreover, the selection of these two NP tests is very similar to that of the Trail Making Test (Parts A and B) and the WAIS-R Digit Symbol sub-test by the AIDS Clinical Trials Group (ACTG) for its ALLRT (ACTG Longitudinal Linked Randomized Trials) study merging cognitive data across multiple ACTG trials to generate data on cognitive performance amongst HIV infected individuals {21}. We predicted that the IHDS would be a valid HAND screening

test in this South African VCT clinic setting, when compared to the combination of the Digit Span and Trail Making Tests.

Measures

International HIV Dementia Scale (IHDS)

The IHDS consists of three items: a timed finger tapping test, a timed alternating hand sequence test, and short-term verbal memory test of four items at two minutes {11}. Each item contributes 4 points to the total score of 12. The IHDS was originally validated in both a US and a sub-Saharan African population (from Uganda). Administration requires approximately 10 minutes. At the cut-off score of 10, the IHDS demonstrated 80% sensitivity and 57% specificity.

Validation of HAND by NP Test Battery

We used a brief NP battery as the standard for validation of HAND diagnosis. Attention was assessed using the Digit Span Forward (DSF) and working memory by the Digit Span Backwards (DSB) sub-tests of the WAIS {22}. Information processing speed was assessed by the Trail Making Test -- Part A (TMT A) and executive function by the Trail Making Test -- Part B (TMT B) {23}. The latter two tests also reflect psychomotor function. We recently published the norms for the above tests derived from HIV seronegative patients attending the VCT clinic at this hospital {24}.

Statistical Analysis

The data were analyzed on JMP 8 software {25}. We constructed two non-parametric receiver operating characteristic (ROC) curves to determine the ability of the IHDS to discriminate HAD and the milder neurocognitive conditions of MND merged with ANI {26}. Using the local NP test norms we developed {24}, we classified patients into ANI/MND or HAD. If a subject had a 1–2 standard deviation (sd) difference on two or more of the four NP tests (DSF, DSB, TMT A, or TMT B), they were classified as “ANI/MND”. Subjects who had a ≥ 2 sd difference on two or more NP tests were classified as “HAD”. These tests represent only the NP criteria for HAND diagnoses; functional status was not assessed and an exclusionary medical work-up for other causes was not conducted {9}. For the IHDS, sensitivity (the true positive rate) and “1 - specificity” (the false positive rate) were computed for each possible score to determine the optimal IHDS cut-off scores for ANI/MND and HAD. We also present the positive predictive value (PPV), the negative predictive value (NPV), and the overall accuracy.

Results

Results of group demographic comparisons are presented in Table 1. Our final analytic sample ($n = 70$, with loss of three from point of recruitment) was comprised predominantly by women (81%). The mean age was 31.5 years ($sd = 7.99$), with no significant differences by HAND grouping. The average level of education was 9.0 years ($sd = 2.88$); the HAD group showed fewer years of education than the neurocognitively normal group ($p = .044$),

in line with previously published work {27}. The mean CD4 cell count was 267 cells/mm³ (sd = 41.7), with no significant differences by HAND grouping.

Using our normative data for the TMT and the DS test together with the diagnostic criteria promulgated at the Frascati Conference {9}, 29% (n = 20) were categorized as ANI/MND and 14% (n = 10) as HAD. The IHDS item and total scores as well as the NP performance on the TMT A, TMT B, DSF, and DSB tests are summarized by HAND disorder groupings (with omnibus ANOVA p values) in Table 1. For all overall group comparisons on the foregoing measures, all but two were statistically significant. Those two scores were the IHDS motor item score (finger tapping) and the DSB score, with the latter showing a trend toward statistical significance.

Specific group contrast comparisons (data not shown) showed a significant difference between the normal group and the ANI/MND group (p = .018) on the IHDS total score. Likewise, there was a significant difference between the normal group and the HAD group (p = .01). There was no statistically significant difference between the ANI/MND group and the HAD group (p = .72). In kind, there were no statistically significant contrast comparisons between those with ANI/MND and those with HAD on any of the IHDS item scores. Although the DSF vs. DSB test contrasts were not statistically significantly different between the ANI/MND and HAD groups, the TMT-A and TMT-B tests did distinguish between the ANI/MND and the HAD groups (p = .014 and .001, respectively).

At the generally recommended cut-off score of 10.0, the ROC model was not statistically significant for ANI/MND in this sample (see Table 2). However, a trend toward significance (p = .06) was shown, yielding a sensitivity of 60% and a specificity of 68%. Overall accuracy was 70% for any level of HAND (ANI/MND merged with HAD) (see Table 3), and 66% for ANI/MND and 66% for HAD (see Table 2). The PPV of the IHDS for ANI/MND was 36–66% with the cut-off score ranging from 11.5 to 7.0. The PPV for HAD was fairly low (16–33%) for the same IHDS range. However, at the cut-off scores of 10.0 and 10.5, the NPVs were 93% and 95%, respectively, for HAD.

To determine the optimal cut-off score for the IHDS to maximize its sensitivity and specificity, additional ROC model analyses were performed at the cut-off score of 10.5. For any level of HAND, a ROC model analysis showed that the IHDS correctly determined presence vs. absence in 69% of cases (p = 0.003), with a sensitivity of 69% and a specificity of 74% (see Table 3). The ROC measure of the Area Under the Curve (AUC) (also referred to as A'), equal to the probability that a classification will rank a randomly chosen positive instance higher than a randomly chosen negative one, was 0.73 for this model – confirming the value of this cut-off score using a separate ROC model outcome measure. A significant model was also obtained at this cut-off score for ANI/MND yielding a sensitivity of 65% and a specificity of 62% (see Table 2 and Figure 1) and for HAD yielding a sensitivity of 80% and a specificity of 60% (see Table 2 and Figure 2).

Discussion

The established prevalence rates of HIV-associated neurocognitive impairment and disorder in sub-Saharan Africa highlight the urgency to develop sensitive and specific screening tests. Based on our abbreviated NP test battery, 43% of this sample showed some degree of neurocognitive impairment – reflecting either ANI/MND or HAD. This finding is quite consistent with findings from Lawler et al., who reported a prevalence of NCI of 38% in Botswana {7}. Thus, we suspect a high prevalence of HAND in sub-Saharan Africa may exist more generally but that HAND nonetheless remains largely undetected, despite the availability of current screening tools.

Results from the ROC model analyses suggest that the IHDS is a suitable and efficient screening test for both ANI/MND and HAD in resource-limited settings, such as HIV VTC clinics in sub-Saharan Africa. While the sensitivity was less for ANI/MND than for HAD, our data suggest that the IHDS is useful across the spectrum of HAND. Further, as aforementioned, the IHDS can be administered within approximately ten minutes. The PPV reflects the percentage of true positive calls by the test being evaluated to the total number of positive calls (i.e., including the false positives) {28} and was fairly low for the IHDS on HAD. The PPV was likely impacted by a number of competing causes of cognitive impairment other than HIV itself in this patient population – including a history of alcohol and substance use, major depressive disorder, CNS opportunistic infections, and the toxic effects of some of the antiretroviral medications themselves, among others. The test sensitivity reflects the percentage of true positive calls by the test being evaluated to the total number of testees with the disease being screened (i.e., including the false negatives). The sensitivity is higher than the PPV, as a false negative test is less likely on the IHDS than a false positive.

Based on our ROC analyses, we recommend that a cut-off score of 10.5 be used in South Africa rather than 10.0, which is the generally recommended cut-off score on this scale {11}. Of note, the standardization article on the IHDS indicated that a cut-off of 10.5 provided even greater sensitivity with a minimal loss of specificity. The fact that the specificity of the IHDS declines rapidly with higher scores suggests the need for the exclusionary medical work-up, as do the low PPVs. In line with these results, the high NPVs across the cut-off scores for HAND indicate that when a person is negative on the IHDS total score, there is a very high probability he/she does not have HAND (as the confound of other medical conditions causing NCI does not impact the negative PPVs). Regarding the lower level of sensitivity we observed for ANI/MND, the scale might be modified to detect milder forms of HAND. One possibility would be to use a longer delay for the word-recall item. Another issue is educational level; possibly, the lower IHDS scores in the HAD group are driven by lower educational level and decreased “cognitive reserve”. We deem this unlikely, however, because additional analyses indicate that significant group differences remain when educational level is included as a covariate (data not shown). In fact, results from the ANCOVAs show no relationships, in general, between educational level and the IHDS total score.

To assess the clinical utility of the IHDS we have discussed several test properties (sensitivity, specificity, PPV, and NPV) by different cut-off scores and severity of HAND. In terms of overall accuracy, it is high in this sample. This is, in part, related to the relatively high prevalence of the disease (HAND) in our sample; since we evaluated the IHDS in patients restricted to an upper limit of CD4 cell count of 350 cells/mm³, HAND prevalence was relatively high. This allowed us to surmount the potential limitation of a high CD4 cell count on test accuracy -- the higher the disease prevalence, the higher the accuracy {29}. We conclude that our results support the use of the IHDS total score for identifying HAND in South Africa -- at least at this range of CD4 cell count. It should be cautioned that these results require confirmation by studies of other HIV infected samples in South Africa as well as other parts of sub-Saharan Africa before they might be considered generalizable to the region.

This study has several additional strengths. We used focused, brief, and culturally neutral NP tests that do not require special instrumentation, and we applied locally validated, published norms. We also accrued a sample representative of the HIV seropositive population in South Africa. The two tests we employed (the TMT and the DS) can be recommended for research studies across a variety of HIV clinical care settings in South Africa to further document their generalizability to the South African population. We selected a sample of patients who were expected to most clearly benefit from effective ART. With a HAND prevalence of 40% in patients within our stipulated CD4 cell count range from 200–350 cells/mm³, we have demonstrated a clear benefit of screening for NCI.

Regarding ARV treatment initiation in the region, the World Health Organization recommends that the CD4 cell count threshold for initiation should be 350 cells/mm³ in 2010 {30} – an increase from the previous recommended threshold of 200 cells/mm³. This recommendation for earlier ARV initiation was adopted in the South African National Guidelines in 2013 {31}. It is also recommended by both sources that clinically symptomatic HIV infection in patients with WHO Stage 3 and 4 disease (which would include HIV-induced cognitive impairment) should be initiated in ARV treatment. Thus, the IHDS would contribute to the decision to initiate ART in this region, directly impacting patient care in this resource-limited setting.

At higher CD4 cell counts there may be too many false positive results generated to warrant screening with the IHDS. Yet, longitudinal study of screening of patients in the higher CD4 cell count ranges (350–500 cells/mm³ and > 500 cells/mm³) may prove justified, especially as the current recommendation in the USA is for universal treatment for HIV infected individuals regardless of CD4 cell count {32} and as this is being advocated more frequently in high-resource countries. Moreover, the associated risk of a false positive screen is not typically clinically significant if the diagnosis is ruled out on a later visit. Given the apparent limits of the IHDS in detecting ANI/MND in this sample, the IHDS and the brief NP validation tests we employed (the DS and the TMT) may be studied for use together in a two-part screening process. In fact, a recently published study from Thailand has demonstrated increased performance when the IHDS was combined with Trails Making Test Part A {33}. Regarding the IHDS, our data suggest that the finger tapping item could be considered for deletion. A focused approach to add NP tests to the IHDS might prove

particularly relevant to increasing the yield of positively screened cases from the South African patient population in the higher CD4 cell count ranges.

This study has several limitations worthy of note. In terms of HAND characterization, we did not include a functional status measure to confirm HAND diagnosis {cf. 9}. In addition and more specifically, we, therefore, could not distinguish between ANI and MND – resulting in their merged consideration here. Future research should examine the sensitivity and specificity of the IHDS for each diagnostic category of HAND (ANI, MND, and HAD) vs. HIV seropositive and seronegative age- and education-matched controls and include a measure of functional status as well as a medical work-up to exclude other medical conditions that might account for NCI. We also did not use a full NP test battery recommended by the Frascati conference criteria {9}. The two NP tests used here were selected to assess the domains of attention, working memory, information processing speed, and executive function. However, this is not equivalent to a comprehensive screening of all neurocognitive domains. Thus, patients with equivocal screening results and/or relevant deficits in functional status in activities of daily living should be referred for more extensive testing. In addition, our sample is relatively small, has a limited age range, and is predominantly female. Yet, this sample is representative of the patient population presenting at HIV VTC clinics in South Africa. With a minor modification in the cutoff score, we conclude that the IHDS is a valid and feasible diagnostic screening test for HAND in clinical settings in South Africa.

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Fig 1. ROC Characteristics for IHDS to Detect ANI/MND

This curve depicts a significant ROC model screening for ANI/MND at a cut-off score of 10.5, yielding a sensitivity of 65% and a specificity of 62%. The AUC statistic for this model was 0.67, further supporting its utility for ANI/MND.

Fig 2. ROC Characteristics for IHDS to Detect HAD

This curve depicts a significant ROC model screening for HAD at a cut-off score of 10.5, yielding a sensitivity of 80% and a specificity of 60%. The AUC statistic for this model was 0.69, further supporting its utility for HAD.

Table 1

Demographics, Screening Test Scores, and Neuropsychological Test Performance

	Normal	ANI/MND	HAD	p
N	40	20	10	
Age	31.52 (6.86)	31.50 (9.68)	31.60 (9.37)	.999
Education	9.62 (2.62)	8.75 (2.94)	7.20 (3.23)	.050
CD4 Cell Count (cells/mm ³)	260 (40.9)	285 (41.7)	259 (37.3)	.067
IHDS Total Score	10.91 (1.16)	9.82 (1.49)	9.40 (2.09)	.002
IHDS Memory-Recall Item	3.76 (0.41)	3.18 (0.77)	3.30 (0.89)	.002
IHDS Psychomotor Speed Item	3.42 (0.71)	2.95 (0.61)	2.90 (1.10)	.030
IHDS Motor Speed Item	3.72 (0.72)	3.70 (0.57)	3.20 (1.23)	.153
Digit Span Forward Sub-Test	6.65 (1.56)	5.00 (0.97)	4.50 (1.35)	.001
Digit Span Backward Sub-Test	3.52 (0.82)	2.95 (0.22)	3.40 (1.78)	.075
Trail Making Test Part A (sec)	45.6 (12.1)	61.3 (27.0)	85.8 (37.2)	.001
Trail Making Test Part B (sec)	77.6 (17.9)	100.0 (26.7)	153.0 (76.0)	.001

Mean (sd)

Table 2
Sensitivity, Specificity, Positive and Negative Predictive Values, and Overall Accuracy of IHDS in detecting ANI/MND versus HAD

Cut-Off Score	ANI/MND				
	Sensitivity	Specificity	PPV	NPV	Overall Accuracy
6.5	.05	0.98	50.00	72.05	0.71
7.0	0.10	0.98	66.66	73.13	0.73
8.0	0.15	0.94	50.00	73.43	0.71
8.5	0.20	0.90	44.44	73.77	0.70
9.0	0.30	0.82	40.00	74.54	0.47
9.5	0.40	0.74	38.09	75.51	0.61
10.0	0.60	0.68	42.85	80.95	0.66
10.5	0.65	0.62	40.62	81.57	0.63
11.0	0.85	0.34	34.00	85.00	0.49
11.5	0.95	0.32	35.84	94.11	0.50
HAD					
6.5	0.10	0.98	50.00	86.76	0.86
7.0	0.10	0.97	33.33	86.56	0.84
8.0	0.20	0.93	33.33	87.50	0.83
8.5	0.20	0.88	22.22	86.88	0.79
9.0	0.40	0.82	26.66	89.09	0.76
9.5	0.50	0.77	26.31	90.19	0.73
10.0	0.70	0.65	25.00	92.85	0.66
10.5	0.80	0.60	25.00	94.73	0.63
11.0	0.80	0.30	16.00	90.00	0.36
11.5	0.90	0.67	31.03	97.56	0.70

Table 3

Sensitivity, Specificity, Positive and Negative Predictive Values, and Overall Accuracy of IHDS in Detecting HAND (ANI/MND and HAD)

Cut-Off Score	HAND				
	Sensitivity	Specificity	PPV	NPV	Overall Accuracy
6.5	0.07	1.00	100.00	58.82	0.60
7.0	0.10	1.00	100.00	59.70	0.61
8.0	0.17	0.97	83.33	60.93	0.63
8.5	0.21	0.92	66.66	60.65	0.61
9.0	0.31	0.87	64.28	62.50	0.63
9.5	0.41	0.79	60.00	64.00	0.63
10.0	0.62	0.76	65.51	73.17	0.70
10.5	0.69	0.74	67.74	76.92	0.73
11.0	0.83	0.39	51.02	76.19	0.59
11.5	0.93	0.39	53.84	88.88	0.63