HIV-associated cognitive disorders: Scientific discoveries through international collaborations in Thailand
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Chapter 10
Trail Making Test A test improves performance characteristics of the International HIV-Dementia Scale to identify symptomatic HAND

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ABSTRACT

Objectives: Although HIV-Associated Dementia (HAD) occurs in less than 5% of individuals with access to combination antiretroviral therapy (cART), rates of milder forms of HIV-Associated Neurocognitive Disorder (HAND) are much higher. We sought to define an optimal cut-point for the International HIV-Dementia Scale (IHDS) for the identification of symptomatic HAND, defined as both HAD and Mild Neurocognitive Disorder (MND). We then sought to determine if adding a simple test from a larger neuropsychological battery could improve the performance characteristics for identifying symptomatic HAND.

Design: A cross-sectional cohort of 75 HIV-infected cART-naïve individuals recruited in Thailand. Methods: Subjects completed neuropsychological tests and underwent a full neurological assessment. HAND diagnoses were determined by consensus conference using the 2007 Frascati criteria, blinded to the IHDS results. The optimal IHDS cut-point was determined by Receiver Operating Characteristic (ROC) analysis with cross-validation. Individual neuropsychological tests were then evaluated and combined with the IHDS to test performance characteristics.

Results: The IHDS was poor at detecting symptomatic HAND at the optimized cut-point of ≤10 (sensitivity: 53.3%, specificity: 89.8%). The Trail Making Test A was most effective in improving performance characteristics when combined with the IHDS, with net sensitivity of 86% and specificity of 79%. Conclusions: In this setting, the IHDS performed poorly in identifying symptomatic HAND, but was substantially improved by the addition of Trail Making Test A, which typically requires less than two minutes to complete. If validated, this combination can address the critical need for HAND screening instruments in international settings.

INTRODUCTION

Since reaching an apex in 1999, the worldwide rate of new HIV infections has fallen by 19%, and access to treatment has increased 13-fold in the past decade. However, these encouraging statistics give way to a hidden truth: the number of individuals in the world living with HIV is now estimated at over
33 million. With increasing life expectancy aided by greater access to antiretroviral treatment, addressing the conditions of chronic HIV infection is of paramount importance.

The propensity of HIV infection to cause neurological and neurocognitive impairment has been well documented.2,3 While the exact mechanism of HIV infection in the central nervous system is not firmly established, the prevalence of cognitive impairment is remarkably high: an estimated 35 - 50% of community-dwelling HIV infected individuals show evidence for HIV-associated neurocognitive disorder (HAND).4,8 Even in settings with access to cART, HAND remains prevalent and while frank dementia (HIV-associated dementia, or HAD) may account for less than 20% of HIV-infected individuals even the milder forms of cognitive impairment have been linked to functional limitations, decreased medication adherence, and mortality.4,5,9-19 Today, more than 80% of cognitively impaired community dwelling HIV-infected patients in the U.S. qualify for a diagnosis of asymptomatic neurocognitive impairment (ANI) or mild neurocognitive disorder (MND) rather than HAD, and we can expect these rates to extend to international settings where access to cART is becoming widespread.10,20 Correctly identifying and diagnosing milder forms of HAND is crucial to developing appropriate treatment strategies.

The current HAND diagnostic criteria classify patients based on cognitive performance and report of functional impairment, with asymptomatic ANI patients lacking functional complaints while individuals reporting functional deficits are categorized as symptomatic MND and HAD.21-23 These diagnostic criteria rely on time-consuming neuropsychological testing, which requires the availability of trained neurologists and neuropsychologists, making the criteria difficult to apply in resource-limited settings. Given that nearly half of all HIV-infected individuals live in low- and middle-income countries, developing a simple screen to identify those with HAND is a key step towards improving diagnoses and care worldwide.1

The HIV Dementia Scale (HDS) was developed in 1995 and later modified for international settings.24,25 A short, easy-to-administer, and reliable screen for dementia, the IHDS has proven successful.5,6,12,20,25-31 However, populations with access to cART are undergoing a shift towards less severe impairment, and an incremental improvement is needed to enhance screening for milder forms of HAND, as the current form of the IHDS substantially restricts its usefulness in resource-limited settings.32,33

Our study focused on a cohort of HIV-infected individuals in Bangkok, Thailand. We sought to define an optimal cut-point for the IHDS to identify all symptomatic HAND (MND and HAD). We also sought to determine if a simple test from our neuropsychological testing battery could be added to the IHDS to improve performance in identifying milder cases of HAND while maintaining efficiency as a screening tool.

METHODS

Participants: All subjects (n=75) were enrolled into one of two studies underway in Bangkok, Thailand (SEARCH 007: NCT00777426 and SEARCH 011: NCT00782808), both designed to investigate markers of cognitive impairment among cART-naïve HIV-infected individuals. All subjects met Thai Ministry of Public Health criteria for initiating cART (CD4 count <350 cells/mm3 or symptomatic disease).34 The SEARCH 011 study (n=61) enrolled subjects stratified by both peripheral blood mononuclear cell HIV DNA levels (>/< 1000 copies of HIV DNA/106 cells) and age (>/< 35 years). Exclusion criteria for both studies were similar and included head injury, illicit drug use, acute illness, pre-existing neurologic or psychiatric conditions, and learning disability. Two participants were excluded shortly after enrollment upon identification of existing infection (toxoplasmosis and tuberculosis); both were subsequently replaced. All subjects signed consent forms approved by the University of California (San Francisco, CA) and the Chulalongkorn Hospital (Bangkok, Thailand) institutional review boards. Trained clinicians conducted the IHDS and were blinded to the results of the subject’s further testing.

Characterization of HAND: Trained nurse-
psychometrists, who were in turn blinded to the IHDS result, conducted the neuropsychological (NP) testing battery, which had been designed for international use as previously described \(^{35}\), and a non-neurologist clinician completed a full neurological examination based on that used by the Adult AIDS Clinical Trials Group. \(^{27,36}\) Individual raw NP scores were transformed to standardized z-scores using normative data from an HIV-negative control cohort evaluated at the same site in Thailand (n=307 initially, increased to 448), although both z-scores and raw scores were considered during diagnostic conference because certain age-education strata from the normative cohort had less than 20 cases. We defined a composite z-score of all tests in our battery as the arithmetic mean of all z-scores (NPZ global). The nurses and physicians separately scored each subject’s level of functional impairment based on semi-structured interviews with the subject and, when possible, proxy informants. A cognitive diagnosis was determined at consensus conference using all clinical data, excluding the IHDS data. Conference participants included a U.S.-trained neuropsychologist (RP), a neurologist (DC), and a geriatrician (VV), all with expertise in HIV.

The 2007 Frascati guidelines for HAND were used as follows: normal (NL): performance on testing that was deemed to be within expectations for age and educational attainment; ANI: performance that was deemed to be lower than could be expected from normal test variation (typically involving at least two domains) but without evidence of functional impairment; MND: performance on testing that was moderately abnormal (typically 1 to 2 SD below the normative data, typically two cognitive domains) and with evidence of functional impairment; or HAD: performance that showed severe impairment (typically worse than -2 SD) in two cognitive domains with clear evidence of functional impairment. Consensus was reached by three investigators (VV, RP, DC) for each case.

Statistical Analysis: Analyses were performed using Stata/IC 12.1 for Windows (StataCorp LP, TX, USA). Pairwise comparisons of the IHDS were completed using nonparametric Mann-Whitney U tests. Hypothesis testing used a significance level of 0.05. We defined three models: Classification I, which distinguished all HAND subjects (ANI+MND+HAD) from normal (NL) subjects; Classification II, which distinguished symptomatically impaired subjects (MND+HAD) from normal and asymptomatic subjects (NL+ANI); and Classification III, which distinguished only the severely impaired subjects (HAD) from all others (MND+ANI+NL). The ability of the IHDS to screen for each classification was assessed by Receiver Operating Characteristic (ROC) analyses with overall performance evaluated using the area under the ROC curve (AUC). The optimal cut-point was determined from sensitivity and specificity. We then cross-validated the IHDS for Classification II by identifying the optimal cut-point in a randomly selected training set of 90% of the subjects (n=68), and then calculated the effective sensitivity and specificity of that cut-point on the remaining test set of subjects (10%, n=7). After ten iterations, sensitivities and specificities were averaged to provide the cross-validated sensitivity and specificity of the IHDS.

In order to improve the performance of the IHDS in identifying symptomatic HAND cases (Classification II), we selected eleven tests from the NP battery, each of which are distinct from tests already part of the IHDS and require ≤5 minutes to complete: Color Trails I and II, Grooved Pegboard dominant and non-dominant hands, Timed Gait, Trail Making Test A, Brief Visual Memory Test – Revised (BVMT-R), Escala de Inteligencia de Wechsler para Adultos (EIVA), digit symbol task (DST), block design, verbal fluency first names and verbal fluency animals. We again used ROC analyses and the AUC to identify the optimal cut-point for identifying symptomatic HAND from the full data set (n=75), rounded to the nearest one-half standard deviation. For the cross-validation of the NP tests, we used training sets of 80% of the subjects (n=60) and test sets of 20% (n=15) because a small test set of 10% did not provide enough variance to validate the test. After five iterations, sensitivities and specificities were averaged to provide the cross-validated sensitivity and specificity of the individual test. We then calculated the cross-validated net sensitivity and specificity of simultaneously applying the IHDS
RESULTS

We enrolled 75 patients between 2008 and 2012. Among these, 42 were female (56%) and the mean (SD) age was 34 (7.0) years. We diagnosed cognitive impairment in 38 subjects (51%), of which 20 (27%) were symptomatically impaired (MND or HAD). No significant differences in demographic or clinical variables were noted between the groups with and without symptomatic HAND (Table 1).

Our initial analysis using Pearson’s correlations identified a moderate association between the IHDS and a composite measure of all neuropsychological tests in our battery (NPZ global) \((r=0.57, \ p<0.0001, \ \text{Figure 1})\); however, mis-categorization of individuals by diagnostic group was apparent, and became more so in ROC analyses.

For the IHDS, the area under the curve (AUC) for Classification III (HAD vs. all others) was greatest compared to other models: 0.944, compared to 0.612 for Classification I and 0.774 for Classification II (Figure 2). In Classification II (symptomatic HAND), the IHDS performed best at the recommended cut-point of \(\leq 10\), however the sensitivity and specificity were only 53.3% and 89.8%, respectively (Table 2). Using the threshold of \(\leq 10\), the IHDS captured 8 of the 9 HAD cases but only 4 of the 11 MND cases.

Among the individual tests in our battery, when analyzed on their own, four emerged with high AUCs for Classification II: Trail Making Test A (0.773), verbal fluency for first names (0.723), Color Trails I (0.709), and Color Trails II (0.709). When simultaneously administered with the IHDS, the Trail Making Test A provided the greatest improvement, increasing sensitivity from 53.3% to 86.0%. The IHDS and Trail Making Test A combined correctly identified 18 out of 20 patients clinically diagnosed with symptomatic HAND, while misclassifying only 11 of the remaining 55 ANI or NL subjects as symptomatically impaired.

When used to distinguish all types of HAND including ANI (Classification I), the IHDS had an AUC of 0.612 with a non-cross validated sensitivity and specificity of 34.2 and 86.5, respectively. The three tests which provided the highest AUC for Classification I were again Trail Making A (0.703),
verbal fluency for first names (0.690), and Color Trails II (0.685).

**DISCUSSION**

Previous studies identify the IHDS as a useful screening tool for severe cognitive impairment, and our findings concur with this conclusion; however, performance for all symptomatic HAND was less favorable, an important shortcoming given the high prevalence of non-HAD impairment. Based on these data, the IHDS cannot be recommended for the identification of HAND.

We show that the addition of a simple test of psychomotor speed, the Trail Making Test A, greatly improved the IHDS for this purpose. This is congruent with pre-cART data identifying psychomotor speed as a sensitive indicator for cognitive impairment. The improvement gained by including this test is particularly encouraging given the ease and speed with which the test may be administered, requiring only a pencil, paper, and stopwatch. Furthermore, the test is non-proprietary.

There are many strengths to our work. The neuropsychological testing battery employed in this study was specifically designed for international use and benefitted from a large sample of normative data with which to interpret impaired performance. The IHDS was administered by non-neurologist clinicians, typical of resource-limited international settings where ready access to neurologists is uncommon. The clinicians and consensus conference investigators were carefully blinded to the results of each other’s data to prevent bias. The consensus conference investigators were not blinded to the individual NP tests used for the second portion of our analysis. While the cross-validation was used to mitigate this bias, the finding with the Trail Making Test A may not be considered a proper validation, and should be repeated in a separate setting.

Neurocognitive testing in international settings may be influenced by cultural factors, and therefore diagnosis which relies solely on test performance may lead to misidentifying cognitively normal patients as impaired. By using culturally appropriate normative data and focusing on patients with known functional impairment, we reduced the likelihood of misclassifying unimpaired subjects. Our decision also reflects the challenges clinicians face with competing demands and limited resources, making asymptomatic conditions a lower priority.

This focus, however, may require broadening. The existing nosology denotes ANI as a distinct category from MND and HAD solely based on identification of functional impairment, but function is often self-reported and subject to inaccuracies. The long-term outcomes associated with ANI have not been conclusively demonstrated, but emerging data suggest similar neuropsychological impairment levels between ANI and MND subjects, and unconfirmed data demonstrate correlations between neuropsychological testing and both brain size and integrity, regardless of the presence of symptoms. Lack of local, culturally appropriate normative data may be an immediate limitation in some settings, but the ease of performing the Trail Making Test A also allows for easy testing of local control subjects.
to estimate normative performance. In the interim, data captured from other settings may be helpful. Similar constraints exist with the IHDS; it has been suggested that the cut-point of the scale should be adjusted to account for the demographics of different populations. In conclusion, the IHDS is a useful tool to screen for HAD; however, it cannot be recommended for identifying all types HAND. In resource-limited clinics, adding the Trail Making Test A to the IHDS is a promising means of improving performance for symptomatic HAND.

REFERENCES


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HIV Dementia, Neuropsychology, Asia, Neuropsychological Tests, Trail Making Test

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