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Trail Making Test A Improves Performance Characteristics of the International HIV-Dementia Scale to Identify Symptomatic HAND

Thep Chalermchai, MD¹, Victor Valcour, MD^{2,3}, Pasiri Sithinamsuwan, MD⁴, Suteeraporn Pinyakorn, MSc⁵, David Clifford, MD⁶, Robert H Paul, PhD⁷, Somporn Tipsuk, RN¹, James L K Fletcher, BM, BCH¹, Victor DeGruttola, ScD⁸, Silvia Ratto-Kim, PhD¹⁰, Nicholas Hutchings², Cecilia Shikuma, MD¹¹, Jintanat Ananworanich, MD, PhD^{1,5,9}, and the SEARCH 007 and 011 study groups

¹SEARCH, The Thai Red Cross AIDS Research Center, Bangkok, Thailand ²Memory and Aging Center, Department of Neurology, University of California San Francisco, San Francisco, CA ³Division of Geriatric Medicine, Department of Medicine, University of California San Francisco, San Francisco, CA ⁴Phramongkutklao Hospital, Bangkok, Thailand ⁵HIV-NAT, The Thai Red Cross AIDS Research Center, Bangkok, Thailand ⁶Washington University in St Louis, Department of Neurology, St Louis, MO ⁷University of Missouri, Department of Psychology, St. Louis, MO ⁸Harvard School of Public Health, Department of Biostatistics, Boston, MA ⁹Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand ¹⁰Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD ¹¹Hawai'i Center for AIDS, University of Hawai'i at M noa, Honolulu, HI

Abstract

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) in Thailand 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. In this study 75 seropositive adults in Bangkok, Thailand, 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 analysis with cross-validation. Individual neuropsychological tests were then evaluated and combined with the IHDS to test performance characteristics. 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%. 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

CORRESPONDING AUTHOR: Victor Valcour, MD, Memory and Aging Center, 675 Nelson Rising Lane, MC: 1207, University of California, San Francisco, San Francisco, CA 94158, vvalcour@memory.ucsf.edu, Tel 415.476.3746, Fax 415.476.0213.

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SEARCH 007 and 011 protocol teams: Nittaya Phanuphak MD, Nitiya Chomchey, Somprarthana Rattanamanee, and Pairoa Praihirunkit from SEARCH/TRCARC; Nijasri Charnnarong MD and Sukalaya Lerdlum MD from Chulalongkorn University; Yotin Chinvarun MD from Phramongkutklao Medical Center; Mark de Souza PhD MPH, Alexandra Schuetz PhD, and Rapee Trichavaroj from the Armed Forces Research Institute of Medical Sciences; Supunee Jirajariyavej MD from Taksin Hospital; Bruce Shramizu MD from the University of Hawai'i and Carol Liu, Elijah Mun, Stephanie Chiao, and Lauren Wendelken from UCSF.

less than two minutes to complete. This combination should be validated in a larger setting since it may address the critical need for HAND screening instruments in international settings.

Keywords

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

INTRODUCTION

Since reaching an apex in 1999, the rate of new HIV infections worldwide has fallen by 19%. Meanwhile, access to treatment has increased 13-fold in the past decade. These encouraging statistics give way to a hidden truth: the number of individuals in the world living with HIV is now estimated to be over 33 million¹. Addressing the conditions of chronic HIV infection is of paramount importance given the increasing life expectancy aided by greater access to antiretroviral treatment.

The propensity of HIV infection to cause neurological and cognitive impairment has been well documented^{2,3}. While the exact mechanism by which HIV infection affects 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^{4,9–11}, and while frank dementia (HIV-associated dementia [HAD]) may account for less than 5% of HIV-infected individuals^{5,10–14}, milder forms of cognitive impairment have been linked to functional limitations, decreased medication adherence, and mortality^{15–19}. 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 cART is becoming widely available^{10,20}. 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 countries¹, optimizing simple screen to best identify both mild and more severe forms of HAND is a key step towards improving diagnoses and care worldwide.

The HIV Dementia Scale (HDS) was developed in 1995²⁴ and later modified for international settings²⁵. A short, easy-to-administer, and reliable screen for dementia, the IHDS has proven successful for the identifying of HAD^{5,6,12,20,25–31}. The IHDS has not been as successful, however, in identifying milder forms of HAND³². Given that populations with access to cART are undergoing a shift towards less severe impairment, the IHDS's capability to screen for all forms of HAND requires assessment and may need an incremental improvement.^{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) in an effort to better understand its utility for milder forms of impairment. 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 and enrolling simultaneously (many individuals co-enrolled in the two studies). 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) whereas the SEARCH 007 study did not apply these restrictions. Subjects underwent comprehensive screening prior to enrollment and 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. Brain MRI and serum tests were completed to identify exclusions and all subjects were required to have a urine toxicology screen. 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 a neuropsychological (NP) testing battery designed for international use, as previously described^{23, 35}. A clinician completed a full neurological examination based on that used by the Adult AIDS Clinical Trials Group²⁷. 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 dataset 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. Using the 2007 published nosology, a U.S.-trained neuropsychologist (RP), a neurologist (DC), and a geriatrician (VV), all with expertise in HIV determined consensus cognitive diagnoses using all clinical data with the exception of the IHDS data.

We applied the 2007 Frascati guidelines for HAND 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 worse 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 for each case.

Statistical Analysis

Analyses were performed using Stata/IC 12.1 for Windows (StataCorp LP, TX, USA). We completed pairwise comparisons of the IHDS using nonparametric Mann-Whitney *U* tests. Hypothesis testing employed 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 symptomatic and 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.

Our full NP battery contains 16 tests, and in order to explore improving the performance of the IHDS in identifying symptomatic HAND cases (Classification II), we selected eleven tests from that full NP battery for further investigation. Each selected test was chosen if it required ≤ 5 minutes to complete, as would be needed for a screening instrument, and is distinct from tests already part of the IHDS: Color Trails I and II, Grooved Pegboard dominant and non-dominant hands, Timed Gait, Trail Making Test A, Brief Visual Memory Test – Revised (BVM-T-R), Escala de Inteligencia de Wechsler para Adultos (EIWA) digit symbol and block design tasks, verbal fluency first names, and verbal fluency animals. We again used ROC analyses and the AUC to identify the optimal cut-point for each test 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 and the NP test.

RESULTS

SEARCH 011 and SEARCH 007 enrolled exactly 75 patients between 2008 and 2012 and all were used in this analysis. 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 correlation identified a moderate association between the IHDS and a composite measure of all neuropsychological tests in our battery (NPZ global) ($r = 0.57$, $p < 0.0001$, 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 10, however the sensitivity and specificity

were only 53.3% and 89.8%, respectively (Table 2). Using the threshold of 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 separately, four emerged with high AUCs for Classification II: Trail Making Test A (0.773, with a cut-point of 1 SD below the norm), verbal fluency for first names (0.723, with a cut-point of -1 SD), Color Trails I (0.709), and Color Trails II (0.709, with a cut-point of -1.5 SD). When simultaneously administered with the IHDS and using a cutpoint of -1 SD on the individual NP tests, the Trail Making Test A provided the greatest improvement. Here, when impairment was identified by scoring less than the determined cut point on either the IHDS (≥ 10) or the Trail Making Test A (≥ 1 SD), the sensitivity of the combined screen was 86.0%, compared to 53.3% for the IHDS alone. The combination of IHDS and Trail Making Test A combined correctly identified 18 out of 20 patients clinically diagnosed with symptomatic HAND, while misclassifying 11 of the remaining 55 cases with ANI ($n=4$) or NL ($n=7$) subjects as symptomatically impaired.

We explored the use of these tests for all types of HAND including ANI (Classification I) in models without cross-validation, where the IHDS had an AUC of 0.612 with 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 HAD, and our findings concur with this conclusion; however, performance for all symptomatic HAND was less favorable. These data identify shortcomings in the use of the IHDS for milder forms of HAND. The current literature on the IHDS focuses largely on identifying the appropriate cut-point in various demographics, and on comparing the scale to other screens for dementia^{36–38}. Among the published studies, there is great variation in how cognitive impairment is defined, but most involve more severe cases. In this study, we identify critical limitations in this screen for milder impairment and extend this work to identify that the addition of a simple test of psychomotor speed, the Trail Making Test A, may greatly improve the IHDS for the purpose of identifying symptomatic HAND. Our finding is congruent with pre-cART data identifying psychomotor speed as a sensitive indicator for cognitive impairment³⁹, however a further validation study is needed as this aspect of our study was developmental. Regardless, 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 and is printed in black and white.

We note important strengths to this 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 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 main limitation to this study was that while making the diagnoses, consensus conference investigators were not blinded to the individual NP tests used for the second portion of our analysis, raising the possibility of circularity. Neuropsychological testing performance impairment beyond one test was required to meet HAND criteria, somewhat mitigating this limitation, and the cross-validation further diminished this bias, however the Trail Making Test A finding should be repeated in a separate validation study considering multiple tests in addition to the Trail

Making Test A. We focused on the IHDS during this study as it has been widely used for the detection of dementia in resource-limited settings, recognizing that the tests which comprise the IHDS may be challenging for untrained clinical workers to conduct reliably, thereby limiting the usefulness of the screen as a whole^{7, 37}.

Neuropsychological 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 impaired⁴⁰. By using tools that minimize cultural bias, having normative data captured locally and focusing on patients with known functional impairment, we reduced the likelihood of misclassifying unimpaired subjects. Our decision to focus on symptomatic impairment for our primary model 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^{41, 42}. 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^{11, 17, 21, 43}. Thus, it is increasingly likely that the asymptomatic aspect of ANI is, at least partly due to lack of insight for deficits.

For some settings, lack of local, culturally appropriate normative data for the Trail Making Test A may be a limitation for immediate implementation of this improvement to the IHDS, 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 helpful⁴⁴. 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^{36, 45, 46}.

In conclusion, the IHDS is a useful tool to screen for HAD; however, it performed suboptimally for milder forms of HAND in this international setting, as has been described with the HDS in the US²⁴. In resource-limited clinics, a validation study adding the Trail Making Test A to the IHDS is recommended since this combination is a promising means of improving performance for the IHDS for identifying symptomatic HAND.

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Figure 1. Correlation between the International HIV Dementia Scale and the global neuropsychological performance (NPZ global score)

* Patient scored -4.45 SD on NPZ Global

Figure 2. Area under the Receiver Operator Characteristics (ROC) of the IHDS
 Classification I: Normal (NL) vs Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV-associated Dementia (HAD); Classification II: (NL & ANI) vs (MND & HAD); Classification III: (NL, ANI, MDN) vs HAD

Table 1

Baseline Demographic and clinical characteristics of the cohort

Characteristics	NL+ANI	Symptomatic HAND	<i>p-value</i>
n (%)	55 (73.3)	20 (26.7)	
Age, mean (SD)	33.9 (7.0)	35.6 (7.3)	0.36
Gender: Female	29 (52.7%)	13 (65%)	0.43
Education, mean (SD)	12.1 (4.6)	10.2 (5.1)	0.13
CD4 (cells/mm ³), mean (SD)	238 (140.4)	188 (140.8)	0.17
HIV RNA (log ₁₀ copies/mL), mean (SD)	4.7 (0.75)	5.0 (0.62)	0.07

Table 2

Overall cross-validated performance of the IHDS (first line), then IHDS plus each test for Classification II

Neuropsychological Test	Cases correctly identified (%)	Sensitivity	Specificity
<i>IHDS alone (cut-off of 10)</i>	12 (60%)	53.3%	89.1%
Trails A	18 (90%)	86.3%	78.8%
Color Trails II	16 (80%)	77.5%	78.8%
Verbal Fluency (<i>first names</i>)	15 (75%)	78.8%	69.1%
Timed Gait	15 (75%)	77.5%	73.9%
EIWA Digits Symbol	15 (75%)	76.3%	78.7%
Color Trails I	14 (70%)	76.3%	79.2%
EIWA Block Design	14 (70%)	71.3%	85.9%
Grooved Pegboard (<i>non-dominant hand</i>)	14 (70%)	70.0%	82.5%
Grooved Pegboard (<i>dominant hand</i>)	13 (65%)	67.5%	84.0%
Verbal Fluency (<i>animal naming</i>) [*]	13 (65%)	66.0%	87.5%
BVMT-R Learning Trials	13 (65%)	75.0%	78.0%

* Cross-validation analysis was not possible for the Verbal Fluency (Animal Naming) test because only 4 subjects scored less than –1 SD below the norm.