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Cognitive Impairment in Zambians with HIV infection and Pulmonary Tuberculosis

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Abstract

Background: HIV-infection may result in cognitive deficits, but the effects of pulmonary tuberculosis (TB+), a common co-morbid condition in HIV infection, on cognition in HIV infections are unknown . Accordingly, we examined the effects of TB+, on neurocognitive functioning in HIV-infected (HIV+) Zambian adults.

Setting: All participants were drawn from HIV clinics in and around Lusaka, the capital of Zambia.

Methods: Participants were 275 HIV+ volunteeers, of whom 237 were HIV+ and TB negative (HIV+/TB-), and 38 also had pulmonary TB+ (HIV+/TB+). Controls were 324 HIV and TB-*uninfected* (HIV-) healthy controls. All HIV+ were prescribed combination antiretroviral treatment (cART). Published, demographically corrected Zambian neuropsychological (NP) norms were used to correct for effects of age, education, sex and urban/rural residence.

Results: NP deficits, assessed by global deficit scores (GDS), were more prevalent in this order: 14% (46 of 324) of HIV- controls, 34% (80 of 237) of HIV+/TB-, and 55% (21 of 38) of HIV+/TB + group. Thus, both HIV-infected groups evidenced more impairment than HIV- controls, and the HIV+/TB+ group had a higher rate of cognitive impairment than the HIV+/TB- group. HIV+/TB+

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patients were more likely to be male, younger, less educated, and have lower CD4 counts and detectable HIV RNA in blood compared to the HIV+/TB- patients.

Conclusion: In HIV infection, TB may contribute to cognitive impairment, even after controlling for lower CD4 counts and viral load. Nevertheless, systemic inflammation from HIV and TB and more advanced immune deficiency at diagnosis of HIV, may contribute to impaired cognition in HIV+/TB+ patients.

Keywords

HIV; Tuberculosis; Inflammation; Neuropsychological performance; Cognitive impairment; Zambia

Introduction

Combination antiretroviral therapy (cART) has greatly reduced the morbidity and mortality associated with HIV infection, but prevalence of HIV associated neurocognitive disorders (HAND) remains elevated, even among virally suppressed patients [1 2]. HAND in these patients is usually only mild to moderate in severety {i.e., Asymptomatic Neurocognitive Impairment and Mild Neurocognitive Disorder [1 3]}, and may not be clinically obvious but can negatively affect everyday functioning, quality of life, and even survival [4 5].

The greatest burden of the worldwide HIV/AIDS epidemic lies in sub-Saharan Africa (SSA). One of the hardest-hit countries in SSA has been Zambia. In 2007, the last demographic survey in Zambia reported that 14.3 % of Zambian adults (16.1% of women and 12.3 % of men) were infected with HIV [6].

The majority of research on HAND has come from Western countries, but in SSA differences higher prevalences of co-infections may contribute to manifestations of HIV central nervous system (CNS) disease, including cognitive impairment. Tuberculosis (TB), the most common serious HIV-related co-infection, is a leading cause of death and disability worldwide. In 2015, one-third of approximately 1.2 million HIV-related deaths were associated with TB [7]. Zambia has one of the highest TB prevalence rates in the world (455/100,000 population), and TB prevalence in HIV positive (HIV+) persons is five times higher than in HIV negative (HIV-) Zambians [8].

Because systemic inflammation that is associated with central obesity appears to contribute to HAND, we hypothesized that pulmonary TB/HIV co-infection might also damage the brain indirectly, that is without CNS invasion by *Mycobacterium tuberculosis*. Cognitive impairment has been associated with the elevated blood levels of the proinflammatory cytokine IL-6 in centrally obese HIV+ patients and HIV-uninfected patients with active pulmonary TB [9 10]. Many other proinflammatory cytokines that increase in pulmonary TB such as INF-alpha or TNF might also contribute to cognitive dysfunction.

Neuropsychological (NP) assessment is an important tool for detecting and categorizing the effects of HIV on the CNS, but until recently, in SSA a lack of population-appropriate normative standards for NP tests has hampered clinical detection and research into HAND [11–13]. This situation has now improved, with the recent publication of age-, education-,

and gender-corrected NP test norms based upon test results of a large sample of healthy, HIV- adults [14].

Here we use the published, Zambian NP norms to compare NP functioning of HIV- controls with that of HIV+ adults without TB (HIV+/TB-) and those with pulmonary TB (HIV+/TB +). The study was conducted in Lusaka, Zambia, where both diseases are common, comorbid conditions. The same NP test battery has been used in multiple other international studies and consistently has been found to be sensitive to effects of HIV infection [2 15–18]. We trained and certified local graduate students, who tested participants in English, the language of the Zambian educational system. Some preliminary NP data related to an HIV+ group that included both TB+ and TB- individuals has been published by Chinyama et al. [19], but without HIV- controls and not in an international journal.

Methods

Design

We compared clinical and cognitive data from a cross-sectional study of cognition in HIV-infected and HIV-uninfected Zambian adults to examine the hypothesis that comorbid pulmonary TB might be associated with greater cognitive impairment in HIV+ patients.

Subjects and Medical Assessments

Participants were drawn from persons attending six medical clinics in Lusaka who were identified by the supervising nurse as potential candidates based on their HIV and TB diagnoses. Of 275 HIV+ patients and 324 healthy HIV- controls, all were18–65 years old, had at least five years of education, and spoke English. All HIV+ participants were urban residents and had been treated with combination anti-retroviral treatment (cART) for more than 3 months. The mean duration for HIV therapy in the HIV+TB- was 2.2 years, while in the HIV+/TB+ group it was 1.6 years.

The participants were divided into HIV-, HIV+/TB-, and HIV+/TB+ groups. Potential participants with extra-pulmonary TB (n=49) were excluded from the present study because of uncertainty regarding this diagnosis. This uncertainty was due to limitations in the necessary medical resources such as histopathological analysis of tissue biopsies in Zambia, which is crucial for a correct diagnosis of extra-pulmonary TB [20].

Pulmonary TB, as an HIV co-infection, was established through a review of medical records for evidence of diagnosis and treatment for pulmonary TB as determined by either a 1) national tuberculosis and leprosy identity card, 2) tuberculosis case number, 3) TB treatment ID card, 4) district health office tuberculosis treatment card or listing in a 5) clinic TB register or 6) TB suspect register.

Of the 38 HIV+/TB+ patients, sputum examined by Ziehl Nielsen Stain for acid-fast bacilli AFB had been positive in 53% (20) and negative in 47% (18). In all smear-negative pulmonary TB cases, CXR was the main supporting diagnostic tool, together with a clinical history consistent with a diagnosis of TB. Cultures and nucleic acid probes for *Mycobacterium tuberculosis* were not used for diagnosis of Zambian TB suspects during the

period of this study. To minimize the effects of symptoms on testing of cognition, all HIV +/TB+ patients were on 4-drug TB treatment regimen for at least 3 month, were responding symptomatically, and were either in intensive or continuous TB treatment phases. The HIV +/TB+ patients were required to be currently free of symptoms suggesting active pulmonary TB, such as prolonged fever, chronic cough, weight loss, malaise, or severe anemia. Neuropsychological functioning was assessed only once. Given that methods to detect MDR-TB in the laboratory were not used in the patients in the present study, we cannot rule out that some may have had drug- resistant TB. The fact that they were still responding clinically after 3 month of TB therapy, however, suggests that they did not harbor MDR-TB. The prevalence of MDR TB in Zambia was estimated to be under 1.8% from 2001 to 2008, with no change over these years [21].

CD4 T-cell counts were enumerated by single-platform flow cytometry, either by Facscalibur or Facscount machines, using standard methods. HIV RNA concentrations (viral load) were measured using the AmpliPrep/COBAS TaqMan HIV-1 test. This method combines automated sample preparation for HIV-1 RNA purification, PCR amplification and detection with the COBAS TaqMan 48 analyzer. Participants were categorized according to whether their HIV viral loads were detectable or undetectable (detection limit at 40 copies/mL). Calibration and quality assessment were conducted according to standard procedures for the instruments.

Healthy Zambian adults of both sexes, and variable age and education (n=324) were tested in order to generate normative standards that allowed us to adjust NP test results for effects of sex, age, education, and urban versus rural residency. Details of the procedures and results of the norming study and inclusion of HIV- participants are reported elsewhere [14 18 22].

Exclusion criteria for both HIV+ and HIV- groups were a history of neurological or psychiatric conditions that could affect cognitive functioning such as epilepsy, closed head injury with loss of consciousness, coma for any reason, encephalitis or other pre-existing neurologic problems, drug abuse, schizophrenia or bipolar disorder, or physical disability. This information was obtained by means of the UC-San Diego HIV Neurobehavioral Research Program's standardized instruments: a) Neurobehavioral Medical Screening Form which assesses medical and neurological histories and b) structured substance use form [15]. Also, the NP differences between the HIV+/TB+ and HIV+/TB- groups remained significant when CD4 counts and HIV viral load were covaried in the analysis. In addition any potential participants who had clinical indications of CNS disorder were excluded from the study.

In order to exclude for major depression and for alcohol and drug use disorders, the study used Psychiatric and Drug Abuse Assessment, which involved the Composite International Diagnostic Interview (CIDI; Version 2.1, World Health Organization), the Beck Depression Scale II [23], and the Substance Use History form [15 24]. The CIDI provides DSM-IV/ICD10 diagnosis of present or past major depression and substance use disorder. The Substance Use (CSS) questionnaire contains a list of drugs and alcohol where the participants were required to state which ones and how much they had used. This form records the quantity, frequency and mode of administration of all substances of abuse that have been used more than five times in the person's lifetime. This information is recorded

for the last 7 days, for the last 8–30 days, for the remainder of the last year, and for the period of peak lifetime use. Moderate alcohol consumption for men was defined as more than 21 units of alcohol per week and 4 units per day. Moderate alcohol consumption in women was defined as being 14 units of alcohol per week and 3 units per day. More than moderate use during the last 30 days was an exclusion.

All participants provided written informed consent to participate in the study. The Biomedical Research Ethics committee at the University of Zambia (UNZABREC) and The Ministry of Health, Zambia approved the study.

Neuropsychological Assessment

Students pursuing a Masters of Science in Clinical Neuropsychology at the University of Zambia performed the neuropsychological testing. They were trained and certified for standardized clinical examination of the participants through theoretical and practical courses. Because English is the primary language of instruction in the Zambian education system, all partcipants spoke English, the language in which the NP testing was performed. Screening for the participants' ability to speak and understand English was performed with the Zambia Achievement Test (ZAT), a test constructed to quantify academic achievement for the purpose of identifying English mastery in Zambian children in grades 1 through 7 [25]. The threshold level of English proficiency for this study was Grade 5 and above. Details for the procedures and results of the norming study and inclusion of HIV- participants are reported elsewhere [14 18 22].

The cognitive domains tested and specific tests were: a) Executive Functioning (Stroop Color–Word Interference trial, Category Test errors, Wisconsin Card Sorting Test – 64 Total errors, and Color Trails 2); b) Working Memory/Attention (Paced Auditory Serial Addition Test – 50 (PASAT); and Wechsler Memory Scale-III Spatial Span Test); c) Speed of Information Processing (Wechsler Adult Intelligence Scale-III [WAIS-III], Digit Symbol, WAIS-III Symbol Search, Trails A, Color Trails 1, Stroop Color Naming and Stroop Word Naming), d) Verbal fluency (Letter fluency, Animal fluency, and Action fluency); e) Learning (Hopkins Verbal Learning Test – Revised) [HVLT-R] and Brief Visuospatial Learning Test – Revised) [BVMT-R]; f) Delayed recall (HVLT-R delay and BVMT-R delay); g) Complex Motor Function (Grooved Pegboard [dominant and non-dominant hands]). These tests have been demonstrated to be sensitive for areas of cognition affected by HIV [26]. The test battery has been used in many international settings related to NP performance in HIV+ participants, in various languages around the world [1 16 27–32]. The tests have all been adapted and normed, with demographic corrections for age, sex, education and urban versus rural residence in Zambia [14].

Statistical Methods

The data were analysed with SPSS Version 24, using ANOVAs and Chi-square tests. Because of multiple comparisons, Bonferroni corrections were performed. The NP tests were combined into 7 functional cognitive domains and summarized as 7 domain T-scores and a (summary) global mean T-score. Some data on the Category and Wisconsin Card Sorting tests were missing for technical reasons. For the 57 subjects who lacked these test

results, their executive and global mean T-scores were calculated with the two remaining executive function tests. In order to examine the influence of immunodeficiency on global cognitive functioning, a univariate analysis was performed with the global mean T-score as the continuous dependent variable and the CD4 count and virus detected or not detected in the blood as covariates.

Seven domain-deficit scores (DDS) and a global deficit score (GDS) summarized performance that was below expected ("impaired") levels for individuals' demographic characteristics by considering only below-expected performance. The GDS categorizes demographically corrected T-scores on a 5-point scale from normal to severely impaired. A deficit score of 0 is normal performance (T-score ≥ 40), whereas a deficit score of 1 is mild impairment (T-score = 35–39), 2 is mild-to-moderate impairment (T-score = 30–34), 3 is moderate impairment (T-score = 25–29), 4 is moderate-to-severe impairment (T score = 20–24), and 5 is severe impairment (T-score < 20). Global NP impairment (HAND) was diagnosed if the GDS was equal to or higher than 0.50, and specific domains score of ≥ 0.5 suggested impairment in that domain. A GDS cutoff of ≥0.50 indicates that the individual on average was at least mildly impaired on at least half of the individual test measures in the entire test battery. The use of this one summary score avoids the problem of multiple comparisons when interpreting or comparing results on a test battery and reflects the number and severity of deficits identified by that test battery. All scores in the normal range (one SD below the normative mean or better) are assigned a deficit score of "0" [33–35]. Unlike a mean T-score or other potential summary scores, the GDS also gives more weight to "problems" (impairments) and protects against the possibility of a very good score on one test obscuring a very bad score on another. Blackstone et al. indicates that the standard GDS cutoff of ≥0.50 also virtually guarantees that the participant will meet Frascati criteria for HAND [3]. It has been used effectively in many studies of neuroAIDS in the US and internationally (including our published work in Zambia).

Results

Demographics and HIV Disease Status

Participants were divided into three groups based on their HIV and TB status, HIV-, HIV+/TB-, and HIV+/TB+. (Table 1). On average HIV- participants were older than HIV+/TB- by 2.6 years, and HIV+/TB+ patients by 6.5 years. HIV- controls also had achieved more years of education on average (11.0) than had HIV+/TB- (10.2) and HIV/TB+ (8.7) groups. The proportion of male HIV+ patients (34%) in our sample was less than that of HIV+ persons in the population in Zambia (42%), based on estimated HIV prevalence of 15% in women and 11% of men [36]. The HIV+/TB+ group consisted of 67% males. Again, these sample demographic differences were controlled using the demographically-corrected neuropsychological test norms (using demographically-corrected T-scores). HIV+/TB+ volunteers had strikingly lower mean CD4 counts than those of HIV+/TB- patients (324 vs 513 cell/ ml), also with all being prescribed cART, they were, nevertheless 3-fold more likely to have detectable HIV levels in blood (53% vs. 17%).

Mood status—We administered the Beck Depression Inventory II (BDI-II) to the HIV infected participants in this study. Their mean score was in the normal to mild area regarding depressed mood. In addition, the TB participants had better BDI-II scores compared to those of the HIV+/TB- . The mean for the HIV+/TB- group was 10.5 (SD 8.5) vs HIV+/TB+ mean of 7.4 (SD 5.5).

Cognitive functioning

Both HIV+ groups performed worse than HIV- controls in 6 of the 7 cognitive domains (all but complex motor skills), and the HIV+/TB+ group was significantly more impaired than the HIV+/TB- participants on tests that represent the same domains, minus executive functions which showed a borderline result (Tables 2 and 3). Mean GDS in the HIV+/TB+ was 0.69 and higher than the HIV- (.25) and HIV+/TB- (.39) groups. Using a GDS ≥ .50 to classify participants as impaired, prevalence rates were 14.2% of the HIV- controls, 33.8% of the HIV+/TB-, and 55.3% of those with HIV+/TB+ ($p < .001$). These NP differences between the HIV+/TB+ and HIV+/TB- groups remained significant when CD4 counts and HIV viral load were covaried in the analyses.

Global mean T-scores correlated modestly with CD4 counts ($r = .142$; $p = .024$) and detectable HIV RNA in the blood (−.146; $p = .021$) in the HIV+ groups. Because the HIV +/TB+ participants had lower CD4 cell counts and higher levels of HIV in their blood, we performed an ANCOVA between the two groups: HIV+/TB- and HIV+/TB+, with the Global mean T-score as the dependent variable and CD4 and HIV viral load as covariates. The ANCOVA identified a significant difference ($p < .003$) between HIV+/TB- participants (n = 212, estimated mean Global T-score = 46.5 (S.E. 0.39) and HIV+/TB+ participants (n = 38, estimated mean Global T-score = 43.3 (S.E.0.98). No significant interactions were seen.

Discussion

In these Zambian volunteers, HIV+ patients with pulmonary TB (HIV+/TB+) were more than three times likely to be cognitively impaired than were HIV- healthy controls (14.2% versus 55.3%) and 1.6 times more likely than HIV+/TB- patients (33.8% versus 55.3%). The HIV+/TB+ group's mean performance was approximately 1 SD below the performance of the HIV- controls on many of the cognitive domains examined. HIV+/TB+ patients were the most impaired when compared to HIV+/TB- in learning (immediate recall), working memory, verbal fluency, memory (delayed recall), and speed of information processing. Executive functions showed a trend in the same direction (p=.06) and fine motor control did not differ between these groups.

The results on the Grooved Pegboard test were not in accord with our expectation that the HIV+ participants would evidence at least some impairment in complex motor skills. However, it has been reported that, in the current era of combination Antiretroviral Therapy (cART), complex motor difficulties are less prevalent in HIV-infected patients than they were in the pre-cART era [37]. Although the HIV+ patients performed better than the HIV – participants in the current study we think this probably is a result of chance. In studies in Ethiopia and Uganda performances on the Grooved Pegboard were similar for the HIV+ and HIV- groups [12 38 39].

HIV infection is associated with increased risk for cognitive dysfunction even in patients on effective treatment, but we cannot be sure if TB acts independently or interacts with HIV to amplify the brain injury assumed to underlie cognitive dysfunction. Additional studies of cognition in HIV+/TB+ and HIV-/TB+ patients are needed to address this question. Likewise, we cannot exclude interactions of TB with other infectious or nutritional (e.g., vitamin D) cofactors in our patients. For example, other co-infections with cytomegalovirus and toxoplasma are associated with increased risk for cognitive impairment in HIV+ patients even when they have no clinical evidence of brain disease [40 41]. The mechanisms for these effects are unclear, but can be mediated by a) Immune deficiency (lower current CD4 counts) in HIV+/TB+ patients), b) elevation of Efavirenz levels by rifampicin, a component of TB therapy, or c) systemic inflammation or immune activation. Low CD4 counts in HIV patients are associated with cognitive impairment [18]. However, in the present study, CD4 counts and TB did not interact, and when controlling for these factors cognitive differences between the two HIV positive groups persisted. In HIV+/TB+ participants may Efavirenz dose-related neurotoxicity contribute to cognitive impairment [42]. It is also known that isoniazide (INH) can cause CNS symptoms, during acute or chronic overdoses [43 44], but the likelihood that these patients were affected by such overdoses at the times of their study participation is considered to be very small.

TB encephalitis and meningitis are uncommon complications of pulmonary TB. If there had been symptoms of CNS infections, the participants would have been referred for brain MRIs. However, TB meningitis may not produce the dramatic symptoms (headache,fever,and delirium) that characterize other more acute forms of bacterial meningitis.Therefore,we cannot rule out that 1 or 2 of our HIV+/TB+ patients might be in early stages of TB meningitis or other CNS opportunistic infections that can diminish cognition. This possibility is however, unlikely to have affected our findings.

The results from the Beck Depression Inventory II (BDI-II) do not suggest that depression contributed to the worse NP performance in the HIV+/TB+ compared to the HIV+/TB- group, because the HIV+/TB+ group had lower average BDI-II scores.

HIV and TB infections each interact with the immune system in multiple overlapping ways [45 46]. Of potential immune mechanisms for their joint mediation of brain injury, increased systemic inflammation appears the most likely for several reasons. Inflammatory conditions such as central obesity elevate blood levels of inflammatory biomarkers (eg, IL-6) and are associated with impaired cognition in both HIV-infected and HIV-uninfected persons [47 48]. Pro-inflammatory biomarkers in blood including IL-6 are elevated at the time of diagnosis of pulmonary TB and decreased with effective treatment [49]. Both active and latent TB infections, increase the risk of acute myocardial infarction, another disease that is linked to systemic inflammation [50 51]. Future studies of cognition in HIV-/TB+ patients should include measures of both systemic and CNS inflammation. Other chronic inflammatory co-infections that can affect cognition such as Hepatitis C, CMV and latent toxoplasmosis, nutritional deficiencies and drugs for TB and HIV infections should also be identified and assessed in these patients as potential confounders.

This study contributes to validation of our English language test battery for cognitive assessments in Zambia. We found similar levels of impairment in HIV patients as found by Heaton and colleagues in five other studies using a similar battery in a variety of settings and languages (Table 4). The prevalence of impairment in HIV+ persons defined as GDS ≥ .50 ranged from 33% to 45% in five other studies using comparable NP test batteries with country-specific, demographically-corrected test norms.

The strengths of this study are its use of a comprehensive battery of cognitive tests that have been validated on HIV patients in multiple settings, and comparison of the performance of HIV+ patients with normative data from HIV- controls from the same country. These norms allow correction for normal effects of age, education, gender, and urban versus rural residence. A potential concern is that the HIV+/TB+ group had significantly lower education than both the HIV+/TB- group and the HIV- control group from which the NP test norms were developed. This could suggest that the demographically corrected NP norms may not have fully corrected for the low level of education in the HIV+/TB+ group. In this regard, it should be noted that the Zambian NP norms provide corrections for age and education as continuous variables, not by relatively small age X education X gender cells. Also, over half of the HIV- adults in the norming group had less than 12 years of education (n=172) and almost a third had education levels less than 10 years (n=105). Thus, people with lower levels of education were well represented in the Zambian norms. Furthermore, education levels (years completed) were not significantly related to mean T-scores in any of the groups in the current study (including HIV+/TB- and HIV+/TB+), so the demographic corrections appear to have successfully removed effects of education level. Also, the NP differences between the HIV+/TB+ and HIV+/TB- groups remained significant when CD4 counts and HIV viral load were covaried in the analyses.

The study's limitations include its 1) cross-sectional design, 2) limited data on details regarding antiretroviral and anti-tuberculosis treatment, 3) relatively small number of pulmonary TB patients, 4) demographic differences among HIV+ groups that could contribute to their poorer performance on testing (although demographically corrected Zambian test norms should correct for these), 5) the study included no HIV negatives with TB, and 6) lack of data on biomarkers of inflammation in blood.

We conclude that the prevalence of impairment in controls and HIV+ patients were consistent with those found in five other international settings using similar assessments. Both HIV and TB appear to contribute to cognitive impairment in our Zambian sample. Patients with pulmonary TB and HIV co-infections have a higher prevalence of neurocognitive impairment (NCI) than do HIV patients without pulmonary TB. NCI could decrease adherence to HIV and TB medications and thus reduce the effectiveness of both treatments in these patients. The higher prevalence of NCI in HIV+/TB+ patients may indicate a need to assist with adherence to medications for treating both conditions and thereby reducing brain impairment. Differences in levels of immune deficiency or systemic inflammation may help to explain differences in the impact of HIV and TB coinfections and should be pursued in future studies.

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Table 1.

Characteristics of the study sample

Demographics and biological markers	HIV- (n = 324) Mean (SD)	HIV+/TB- (n = 237) Mean (SD)	*p*-value between HIV- and HIV+ only	HIV+/TB+ (n = 38) Mean (SD)	*p*-value between HIV+/TB- and HIV+/TB+
Age	38.5 (12.8)	41.1 (8.8)	.006	34.9 (7.3)	.001
Education in years	11.0 (2.6)	10.2 (2.2)	<.001	8.7 (2.4)	<.001
Gender: Males/females	157/167	81/156	.001	25/13	<.001
CD4 count	----	513.2 (260.6)	----	323.6 (177.2)	<.001
Virus load detected (above 40 copies/mL) no/yes	-----	(N = 212) 178/34 (16%)	----	18/20 (53%)	<.001

HIV- is no HIV infection. HIV+/TB- are participants who only are infected with HIV. HIV+/TB+ are participants infected with both HIV and TB.

Table 2.

Neuropsychological tests across 3 groups.

Neuropsychological tests	HIV- controls, mean (SD), N = 324	HIV+/TB- mean (SD) N = 237	*p*-value between HIV- and HIV+/TB-	HIV+/TB+ mean (SD) N=38	*p*-value between HIV +TB- and HIV+/TB+
Category test●	50 (9.8)	44.1 (8.6),	**<.001**	42.6 (7.8)	1.00
Wisconsin Card sorting●	50 (9.8)	44.1 (10.1)	**<.001**	44.7 (10.0)	1.00
Stroop Interference	49.6 (10.0)	48.1 (10.0)	0.30	47.7 (12.6)	1.00
Color Trails 2	49.6 (9.9)	48.2 (9.5)	0.23	40.0(9.0)	**<.001**
FAS fluency	49.7 (10.0)	46.0 (10.7)	**<.001**	39.7 (10.6)	**.001**
Animal fluency	49.4) (10.1)	48.7 (11.1)	1.00	46.3 (9.3)	.55
Action fluency	49.6 (9.9)	45.6 (10.8)	**<.001**	38.6 (9.5)	**<.001**
Trail Making A	49.9 (9.9)	47.0 (10.0)	**.002**	44.3 (8.2)	.40
Color Trails 1	49.6 (9.6)	49.0 (9.8)	1.00	47.6 (8.4)	1.00
Digit Symbol	49.7 (10.1)	43.5 (10.0)	**<.001**	37.1 (10.3)	**.001**
Symbol Search	49.9 (10.1)	44.5 (10.7)	**<.001**	37.5 (9.9)	**<.001**
Stroop word	49.5 (9.7)	46.8 (11.0)	**.007**	43.1 (9.5)	.11
Stroop color	49.6 (10.0)	48.2 (11.0)	.40	44.0 (9.8)	.07
PASAT	50 (9.7)	46.3 (10.8)	**<.001**	39.1 (10.6)	**<.001**
Spatial Span	49.5 (9.8)	43. 1 (10.9)	**<.001**	40.1 (13.3)	.28
Hopkins Verbal Learning test (learning)	50.0 (10.0)	45. 7 (9.3)	**<.001**	39.1 (7.1)	**<.001**
Brief Visual Memory test (learning)	50.0 (10.2)	43.9 (10.2)	**<.001**	39.5 (9.6)	**.04**
Hopkins Verbal Learning test (delayed recall)	49.6 (10.0)	46.6 (9.9)	**.001**	41.9 (6.6)	**.02**
Brief Visual Memory test (delayed recall)	50.0 (10.2)	44.7 (10.2)	**<.001**	40.0 (9.3)	**.03**
Grooved Pegboard DH	49.8 (10.0)	52.5 (11.2)	0.009	52.6 (9.2)	1.0
Grooved Pegboard NDH	49.9 (10.1)	51.4 (12.0)	1.00	51.3 (10.3)	1.0

HIV- are HIV negative controls. HIV+/TB- are participants infected with HIV only. HIV+/TB+ are participants with both HIV and TB. Age, education, gender, and urban/rural corrected T-scores are used; *p* values for comparison of mean differences between each HIV+ and groups reported with post hoc Bonferroni corrections are reported. The HIV+/TB+ participants performed significantly worse than the HIV- participants on all tests except Color trails 1, Stroop color word interference, Animal fluency, and Grooved Pegboard test.

● Forty seven HIV+ had missing data on these tests.

Table 3.

Neuropsychological Domain mean T-scores and Mean Global T-scores across 3 groups. Low score worse performance.

Neuropsychological ability domains	HIV- controls, mean T-scores (SD), n = 324	HIV+/TB- only, mean T-score (SD), n = 237	*p*-value between HIV- and HIV+/TB-	HIV+/TB+, mean T-score (SD), n = 38	*p*-value between HIV+/TB- and HIV+/TB+
Executive functioning	49.8 (6.3)	46.4 (6.5)	<.001	43.7 (5.8)	.06
Verbal Fluency	49.6 (7.0)	46.8 (7.9)	<.001	41.9 (6.3)	<.001
Speed of information processing	49.7 (7.0)	46.4 (7.4)	<.001	42.1 (6.9)	.002
Working Memory	49.8 (7.2)	44.7 (8.4)	<.001	39.6 (8.7)	.001
Learning/immediate recall	50.0 (7.9)	44.8 (7.9)	<.001	39.3 (7.5)	<.001
Delayed recall	49.8 (8.0)	45.6 (8.2)	<.001	40.9 (5.7)	.002
Fine motor control	49.9 (9.2)	51.9 (10.7)	.05	52.0 (9.2)	1.00
Global Deficit Score	49.8 (5.1)	46.6 (5.8)	<.001	42.8 (5.1)	<.001

HIV- are HIV negative controls. HIV+ are HIV positive participants without TB. HIV/TB are HIV positive participants with pulmonary TB.

Table 4.

HAND prevalence in other international settings using the same neuropsychological test battery.

Region	N	Age (Mean, SD)	Education (Mean, SD)	% Male	NCI Prevalence
US	947	40.5 (9.4)	12.9 (2.5)	69%	36%
Anhui	199	40.3 (6.2)	5.9 (2.1)	63%	35%
Yunnan	403	35.8 (5.8)	9.8 (2.4)	66%	39%
India (Pune)	246	32.1 (8.0)	10.3 (3.5)	57%	45%
India (Chennai)	69	37.4 (8.1)	10.2 (2.9)	68%	33%
Zambia	366	37.4 (12.7)	11.0 (2.5)	48%	35%