Assessing Neurocognitive Impairment in HIV-positive Patients: The Sensitivity and Specificity of the CogState Brief Battery

by

Nirupama Yechoor

Duke Global Health Institute
Duke University

Date:_____
Approved:

_____
Christina Meade, Supervisor

_____
Daniel Westreich

_____
Kevin Robertson

Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science
in the Duke Global Health Institute
in the Graduate School of Duke University

2012

Abstract

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Abstract

Objective: The prevalence of cognitive impairment in HIV-positive patients is estimated to be 39% in Uganda [1]. Despite the high prevalence of impairment, routine HIV management in Uganda does not include neuropsychological assessment. The objective of this study was to compare performance on the gold standard neuropsychological exam and on the CogState computerized exam. We hypothesized that there would be a high degree of correlation between performance on the two exams.

Methods: This cross-sectional survey was conducted from August to October 2011. Each participant completed the standard neuropsychological exam, which consisted of 10 tasks across 7 cognitive ability domains. Patients also completed CogState, which consisted of 4 tasks using playing cards. Performance for each exam was standardized using normative data from HIV seronegative controls to produce z-scores. The primary outcome measures were average z-scores of performance for each exam.

Results: Out of 181 patients tested, 130 (72%) were classified as impaired on the gold standard neuropsychological exam, while 104 (57%) were classified as impaired on CogState. The sensitivity of CogState compared to the gold standard was 65% (95% CI = 56% - 73%) and the specificity was 63% (95% CI = 48% - 73%). The Pearson's correlation of cumulative performance between the exams is 0.552, which is significant at the 0.01 level. Finally, those patients with normal cognition performed the best on CogState, while those with the most severe impairment performed the worst.

Conclusions: Our findings suggest that CogState is a feasible and useful tool to screen for and monitor impairment in HIV-positive patients, especially in resource-

limited settings. Future studies are needed to examine how individual performance on CogState changes over time.

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1 INTRODUCTION

With advances in our understanding of HIV/AIDS biology and the increasing availability of highly active antiretroviral therapy, the mortality and morbidity from HIV infection has decreased [2]. In the sub-Saharan country of Uganda, rates of HIV infection have decreased in recent years, and World Health Organization (WHO) efforts have helped increase the availability of HAART to treat over half of the population that requires treatment [3].

However, even with declining rates of infection and increased access to treatment, new clinical challenges are becoming apparent as HIV-positive patients are living longer. Despite viral suppression, HAART does not fully restore health, and patients are at high risk for neurocognitive disorders [2]. Although HIV-associated neurocognitive disorders have been well documented in Uganda, routine HIV care and management does not include cognitive assessments [4]. This project investigated a novel tool to potentially better screen for and monitor neurocognitive impairment in the HIV-positive population.

2 BACKGROUND

Neurocognitive impairment (NCI) associated with HIV has been well documented in Uganda, yet cognitive assessments are not included in routine care and management of HIV-positive individuals [4]. The manifestation of NCI may affect multiple cognitive ability domains including verbal learning and memory, attention, executive function, speed of processing, sensory-perceptual skills, and motor skills [5]. Studies in Uganda have reported a total prevalence of 39% impairment of any severity, and 26% prevalence of moderate cognitive impairment [1]. Similarly, a recent study in Botswana reported that 38% of patients were classified as impaired despite almost 97% of those patients receiving antiretroviral treatment [6], suggesting that NCI persists even if patients receive treatment.

The gold standard neuropsychological assessment for cognitive impairment is a battery of paper and pencil tests that examine the 7 cognitive ability domains [5]. In Uganda, the standard battery consists of 10 exams, and requires at least 1 hour to complete. At Ugandan clinics with high patient-provider ratios and upwards of 300 patient visits a day [7], routine administration of the standard battery is infeasible. Additionally, if administered multiple times, performance on the standard exam is susceptible to practice effects [8-10], which may mask cognitive decline as increasing familiarity with the tasks leads to improved performance.

Thus, another method is needed for rapid screening for neurological impairment in this population. One alternative is the International HIV Dementia Scale, which has been used successfully in sub-Saharan Africa [6] and was developed specifically for rapid screening [11]; however, the practice effects of this exam have yet to be determined. One

better alternative may be the CogState Brief Battery, a computerized exam that has been developed to screen and monitor impairment in HIV-positive populations [12]. This instrument is easily administered, can collect data from large samples, is not susceptible to practice effects [13], and is much shorter than the standard assessment; thus it may be a useful tool to measure cognitive functioning in HIV-positive patients in resource-limited settings.

The CogState Brief Battery has been validated in HIV-positive patients in the United States; however, it has not yet been validated for this population in Uganda [12]. The purpose of this study was to compare performance on the gold standard neuropsychological battery with performance on the CogState Brief Battery in HIV-positive patients in Kampala, Uganda.

3 METHODS

Study Participants

We conducted this cross-sectional survey from August 2011 until October 2011 in Mulago Hospital of Makerere University in Kampala, Uganda. We recruited 181 HIV-positive subjects from the Infectious Disease Clinic. Eligibility criteria were ages of 18-50 years, ability to read English, no history of neurological or psychiatric illness unrelated to HIV. Ethical approval was obtained from Duke University, the Infectious Disease Clinic, and Makerere University. Written informed consent was obtained from all participants prior to all study-related activities.

Instruments

The standard neuropsychological test battery was chosen for its cultural independence and has been previously administered in an HIV-positive population in Uganda [14-16]. The individual tests assess function over seven cognitive ability domains: Verbal Learning/Memory (WHO/UCLA Auditory Verbal Learning Test) [17], Attention and Working Memory (Digit Span Forwards and Backwards) [18], Speed of Information Processing (Color Trails 1), Executive Functioning (Color Trails 2) [19, 20], Sensory-perceptual motor skills (Grooved Pegboard) [21], and Gross Motor skills (Finger Tapping) [22]. These tasks are summarized in Table 1.

Table 1: Summary of Standard Neuropsychological Exam and Normative Data

Gold Standard Neuropsychological Exam (ability domain)	Instructions	Normative Data
WHO/UCLA Auditory Verbal Learning Test (verbal learning and memory)	Recall as many words as possible from 9 trials	Ugandan HIV seronegative cohort (Robertson et al. 2007)
Digit Span: forwards and backwards (attention and working memory)	Repeat series of numbers (in order or reverse order)	
Color Trails 1 (speed of information processing)	Make a trail from 25 circles, starting from 1 and proceeding sequentially to 25	
Color Trails 2 (executive functioning)	Make a trail from 25 circles, starting from 1 and proceeding sequentially and alternating color	
Grooved Pegboard: dominant and non-dominant (sensory-perceptual motor skills)	Manipulate pegs to fit them into correct grooves	
Finger Tapping: dominant (gross motor skills)	Tap index finger of dominant hand as fast as possible for 10 seconds, repeat for 5 consecutive trials	Ethiopian HIV seronegative cohort (Clifford et al. 2007)

The CogState Brief Battery was administered on a laptop computer and consists of four tasks using playing cards. For each task, the participant focused on a playing card in the center of the screen, and then pressed one of two keys on the keyboard to respond either "yes" or "no". The first task was the Detection Task; a simple reaction-time test in which the participant must follow the rule "Has the card turned face up?" Next, The Identification Task is a choice reaction-time test in which the participant must follow the rule "Is the face-up card red?" The third task is One-Card Learning, which requires that the participant to follow the rule "Have you seen this card before in this task?" The last task is One-Back that requires the participant to follow the rule "Is this card the same as the previous card?" The primary outcome measure for the first two tasks, Detection and Identification, was reaction time. The primary outcome measure for the third and fourth

tasks, One-Card Learning and One-Back, was accuracy. These tasks are summarized in Table 2.

Table 2: Summary of CogState tasks and Normative Data

CogState (main outcome measure)	Instructions (press Yes or No)	Normative Data
Detection (reaction time)	Has the card turned face up?	CogState HIV seronegative cohort
Identification (reaction time)	Is the face-up card red?	
One-Card Learning (accuracy)	Have you seen this card before in this task?	
One Back (accuracy)	Is this card the same as the previous card?	

The order of administering the standard exam or CogState was randomized across participants. Each participant also completed a sociodemographic survey, a medical history questionnaire, and the International HIV Dementia Screen.

Data Treatment

Raw scores for individual tasks in both the standard exam and CogState were normalized to produce z-scores by subtracting the mean test scores from the normative, HIV seronegative referent population, and then dividing by the referent standard deviation (SD). Therefore, z-scores have a mean of 0, an SD of 1, and negative z-scores denote below average performance. Performance on the standard neuropsychological battery was compared to normative data from HIV seronegative patients in Uganda and Ethiopia (Table 1). Normative data for the CogState battery was obtained from CogState and comprised age-matched, HIV seronegative controls from America (Table 2).

For the standard battery, after z-scores were obtained for each task, they were multiplied by 10 and added to 50 to obtain T-scores. T-scores are also standardized scores but have a mean of 50, an SD of 10, and a T-score of below 50 denotes below

average performance. T-scores were then converted to the Deficit Score, a numerical scale ranging from 0 to 5, as follows: $T \geq 40 = 0$, $39 \geq T \geq 35 = 1$, $34 \geq T \geq 30 = 2$, $29 \geq T \geq 25 = 3$, $24 \geq T \geq 20 = 4$, $T < 20 = 5$. A Deficit Score of 0 is classified as normal performance, and a Deficit Score of 5 is severe impairment. The 9 Deficit Scores for all tasks were averaged and then rounded to the nearest integer to obtain the Global Deficit Score (GDS)[23]. Note that the z-scores for Grooved Pegboard, Color Trails 1, and Color Trails 2 were all multiplied by (-1) so that positive z-scores indicate above average performance and negative z-scores indicate below average performance.

For CogState, the z-scores were averaged to obtain the quantitative neurological performance z-score, or QNPZ-score [24]. Note that the z-scores for the reaction time tests for CogState (Detection and Identification) were multiplied by (-1) so that positive z-scores indicate above average performance and negative z-scores indicate below average performance.

Classification of Impairment

We made a dichotomous, "impaired/unimpaired" classification on the standard neuropsychological battery as follows: if participants performed less than 1 SD below the mean in at least 2 cognitive ability domains *or* performed less than 2 SD below the mean in at least 1 ability domain, they were classified as impaired; otherwise, they were classified as unimpaired [5]. Similarly, a dichotomous, "impaired/unimpaired" classification was made using CogState: if participants performed less than 1 SD below the mean on 2 or more tasks, they were classified as impaired [25]. This particular cutoff for CogState has been previously shown to have the highest sensitivity compared to using

cutoffs of performing 1.65 SD or 2 SD below the mean on 2 or more tasks; however, we conducted a separate analysis to further examine other cut-offs, which could have different sensitivity and specificity.

To classify impairment using the GDS, we assigned patients to a clinical impairment category. Those patients with a GDS of 0 were classified as normal, those with a GDS of 1 were classified as having mild impairment, those with a GDS of 2 were classified as having mild to moderate impairment, and those with a GDS of 3 were classified as having moderate impairment.

Data Analysis

We used chi-square tests and student t-tests to compare demographic indicators between those who were impaired or unimpaired on the standard exam. A Pearson's correlation was used to compare cumulative performance on the standard neuropsychological exam with cumulative performance on CogState.

4 RESULTS

Demographics and Impairment

Of the 181 patients, 58% were female, the median age was 37 (inter-quartile range: 31 - 43); 80% were being treated with antiretroviral therapy. The majority of participants (72%) were classified as impaired using the standard neuropsychological battery. Additional details are given in Table 3.

Table 3: Demographics classified by impairment on standard neuropsychological exam.

Demographics	Total (n=181) n (%)	Unimpaired (n=31) n (%)	Impaired (n=150) n (%)	p-value
Mean Age (SD)	36 (8)	32 (8)	38 (8)	<0.001
Median Age (IQR)	37 (31-43)	32 (24-39)	39 (35-43)	
Sex (Female)	105 (58%)	30 (59%)	75 (58%)	0.890
Handedness (Right)	168 (93%)	48 (94%)	120 (92%)	0.180
Education				
Only Primary	14 (8%)	2 (4%)	12 (9%)	0.005
Some Secondary	101 (56%)	21 (41%)	80 (62%)	
Full Secondary	66 (36%)	28 (55)	38 (29%)	
Mean Income (SD)	186,141 (232,188)	186,608 (214,780)	185,958 (239,468)	0.987
Median Income (IQR)	100,000 (10,000-300,000)	100,000 (0-280,000)	100,000 (15,000-300,000)	
Main Language Spoken				
English	17 (9%)	7 (14%)	10 (8%)	0.076
English & Other	52 (29%)	17 (33%)	35 (27%)	
Luganda	87 (48%)	17 (33%)	70 (54%)	
Other	25 (14%)	10 (20%)	15 (12%)	
History of Syphilis	61 (34%)	16 (31%)	45 (35%)	0.678
Current Neuropathy	43 (24%)	8 (16%)	35 (27%)	0.110
History of Tuberculosis	64 (35%)	12 (24%)	52 (40%)	0.037
History of Neurotoxic Drugs	155 (85%)	43 (84%)	112 (86%)	0.751
WHO Stage				
1	11 (6%)	7 (14%)	4 (3%)	0.017
2	49 (28%)	14 (29%)	35 (27%)	
3	61 (34%)	18 (37%)	43 (33%)	
4	57 (32%)	10 (20%)	47 (36%)	
Mean CES-D score (SD)	7 (9)	6 (9)	7 (9)	0.601
ARV Regimen				
Combivir & Nevaripine	60 (33%)	20 (39%)	40 (31%)	0.122
Combivir & Efavirenz	44 (24%)	8 (16%)	36 (28%)	
None	36 (20%)	14 (27%)	22 (17%)	
Other	41 (23%)	9 (16%)	32 (25%)	
Mean current CD4 (SD)	432 (218)	444 (228)	428 (215)	0.662
Median current CD4 (IQR)	405 (269-586)	409 (272-583)	401 (269-586)	
Mean Nadir CD4 (SD)	140 (117)	151 (148)	136 (106)	0.556
Median Nadir CD4 (IQR)	124 (55-195)	138 (67-181)	120 (49-206)	
Mean IHDS (SD)	9.9 (1.5)	10.6 (1.2)	9.7 (1.5)	<0.001

SD = standard deviation; IQR = inter-quartile range; UGX = Ugandan Shillings, where 100,000 is approximately $40 US dollars; CES-D = Center for Epidemiological Studies Depression Scale; IHDS = International HIV Dementia Scale.

Comparison of CogState and the Standard Neurological Battery

The Pearson's correlation between cumulative performance on the standard battery and cumulative CogState performance is 0.552 ($p<0.0001$). When using a

dichotomous, “impaired/unimpaired” classification, 130 out of 181 participants (72%) were classified as impaired on the standard exam. Compared to those who were unimpaired on the standard exam, those who were impaired tended to be older, have a lower level of education, have a history of tuberculosis, and were more likely to be classified in WHO Stage 3 or 4 (Table 3). Of note, there was no difference in the number of patients impaired between those being treated with antiretroviral therapy compared to those who were not (Table 3).

Using CogState and the baseline dichotomous definition of impairment, 104 out of 181 participants (57%) were classified as impaired. Using this dichotomous, “impaired/unimpaired” classification and taking the standard neuropsychological battery as a gold standard, the sensitivity of CogState was 65% (95% CI 56% - 73%) and the specificity was 63% (95% CI 48% - 73%).

Next, we compared the cumulative CogState performance between those who were impaired on the standard neuropsychological battery to those who were unimpaired; those who were impaired performed worse on CogState than those who were unimpaired (Figure 1). CogState performance was on average less than 1 SD below the mean for those who were impaired, which was significantly lower than the CogState performance for those who were unimpaired (Figure 1).

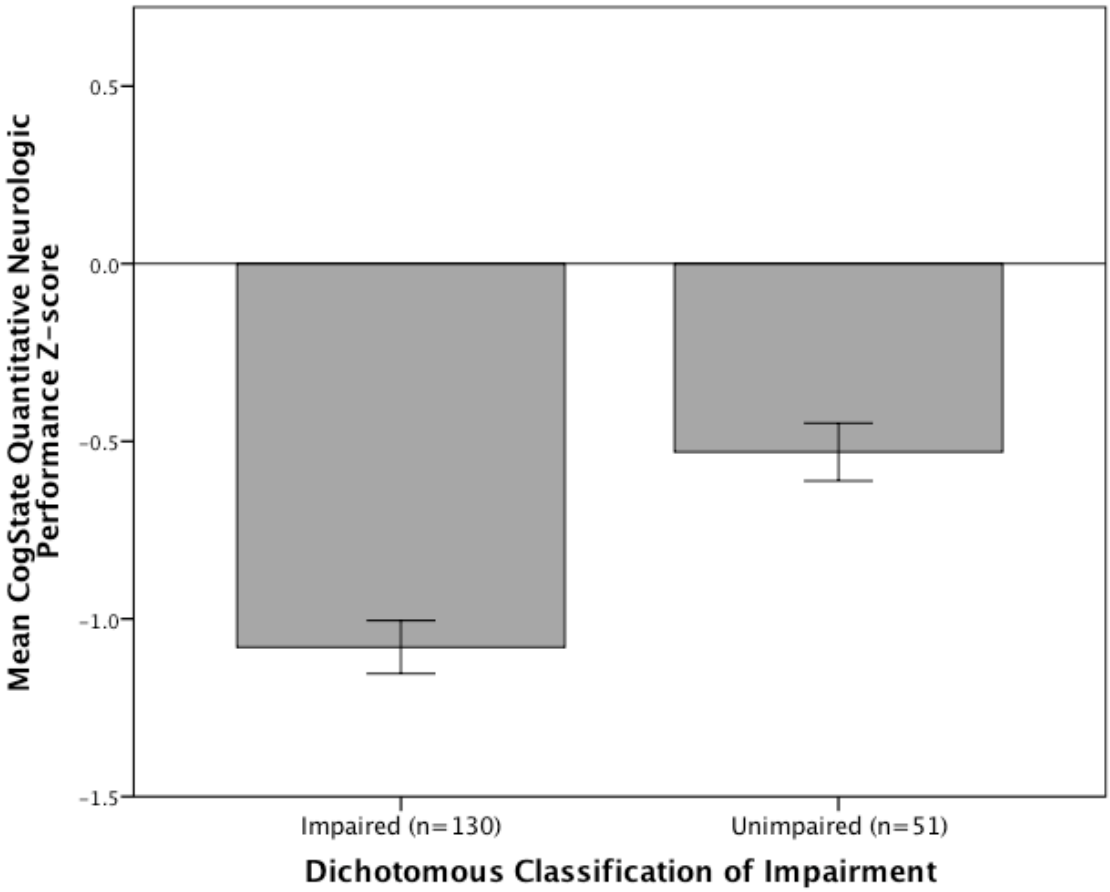


Figure 1. Mean CogState Performance by Impairment on the Standard Neuropsychological Exam. Impairment is classified as performing 1 standard deviation below the mean on 2 or more ability domains or performing 2 standard deviations below the mean on 1 or more ability domains. The mean CogState QNPZ-score for those patients who are impaired is -1.08, and the mean CogState QNPZ-score for those patients who are unimpaired is -0.05. The difference in means is statistically significant with a p-value of <0.001. The mean difference is -0.55 (95% confidence interval: -0.81 to -0.2).

When performance on the standard battery analyzed by the Global Deficit Score, 47% (85/181) of participants were classified to a clinical impairment category. The rest of the participants (96/181) were classified as normal. We then compared performance of all participants on CogState by the GDS clinical impairment category, and found that participants who were classified as normal had the best CogState performance (Figure 2). Similarly, those who were classified as having moderate impairment (the worst level of

impairment observed), performed the worst on CogState. However, when using the QNPZ-scores on the standard neurological battery, 100% of participants performing 1.5 SD or less than the mean were also classified as impaired on CogState. Similarly, no participant performing 0.5 SD or greater than the mean was classified as impaired on CogState (Figure 3).

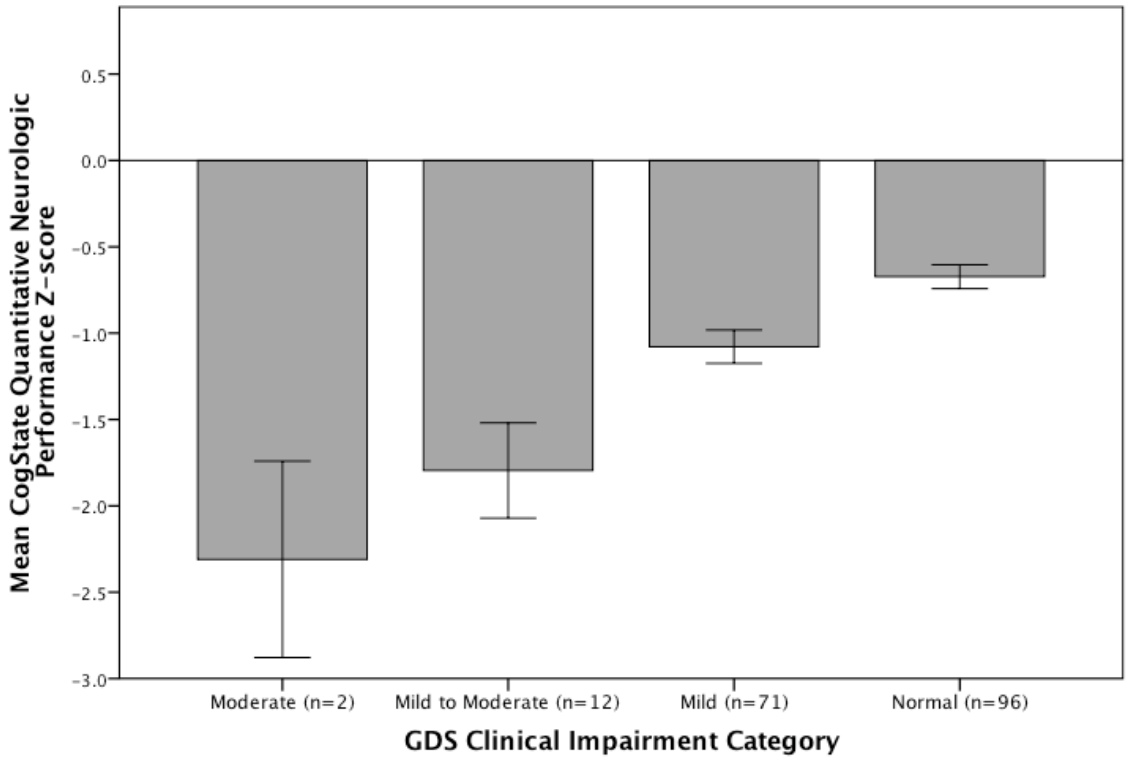


Figure 2. Mean CogState Performance by GDS Clinical Category. The GDS clinical category is the average of deficit scores across each task from the standard neuropsychological exam. A GDS of 0 is classified as normal cognition, while a GDS of 3 is categorized as moderate impairment. Participants classified as normal have the highest mean CogState performance. Participants with moderate impairment have the poorest mean CogState performance.

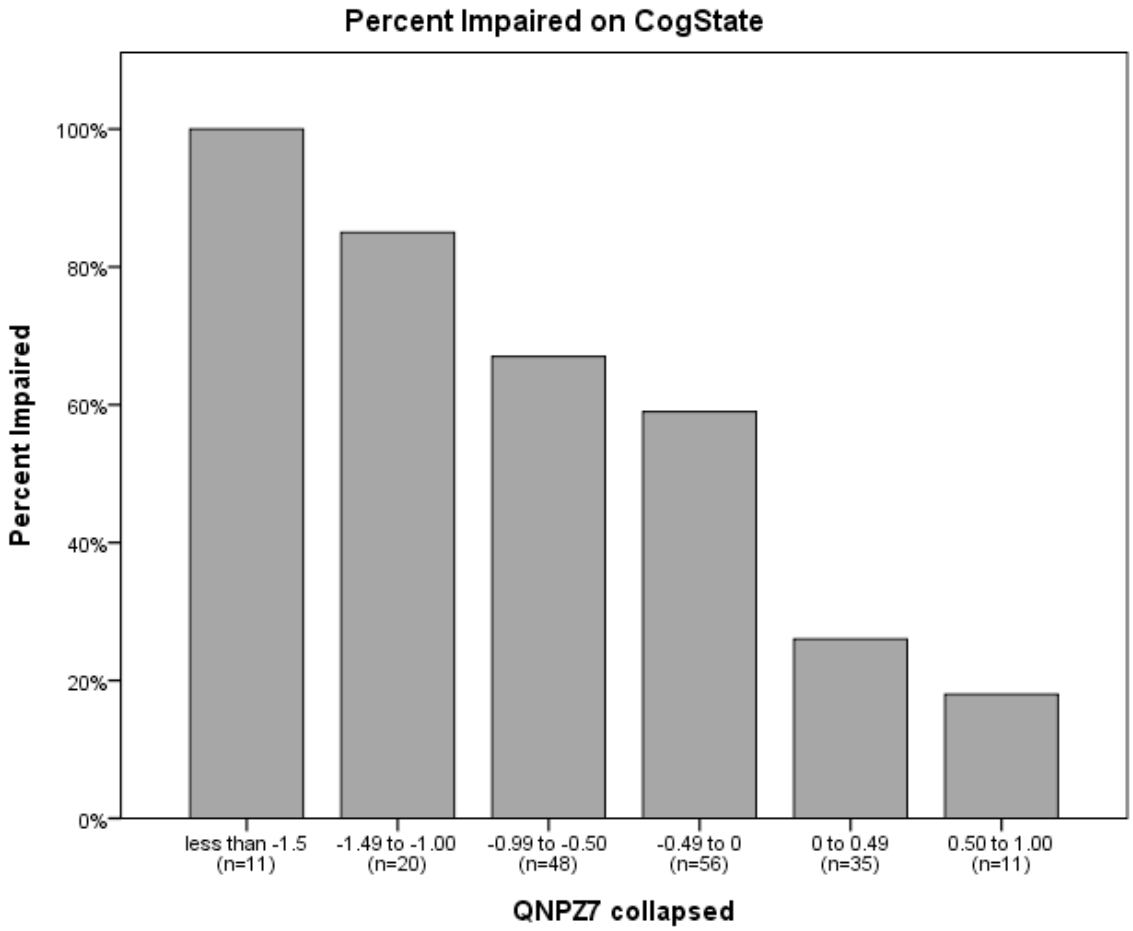


Figure 3: Percent of participants impaired on CogState by performance on standard neuropsychological battery. Impairment on CogState is classified by performing 1 or more SD below the mean on at least 2 tasks. All participants performing less than 1.5 SD below the mean on the standard exam are impaired on CogState. No participant performing 0.5 SD above the mean is impaired on CogState.

When performance on both CogState and the standard battery are normalized an analyzed by each CogState task, participants who performed above zero on the standard battery had and average CogState performance of below zero on the Detection and Identification tasks (Figure 4a). This trend is not apparent in the One-Card Learning or One-Back tasks, where those who perform above zero on the standard exam also have above zero CogState performance (Figure 4b).

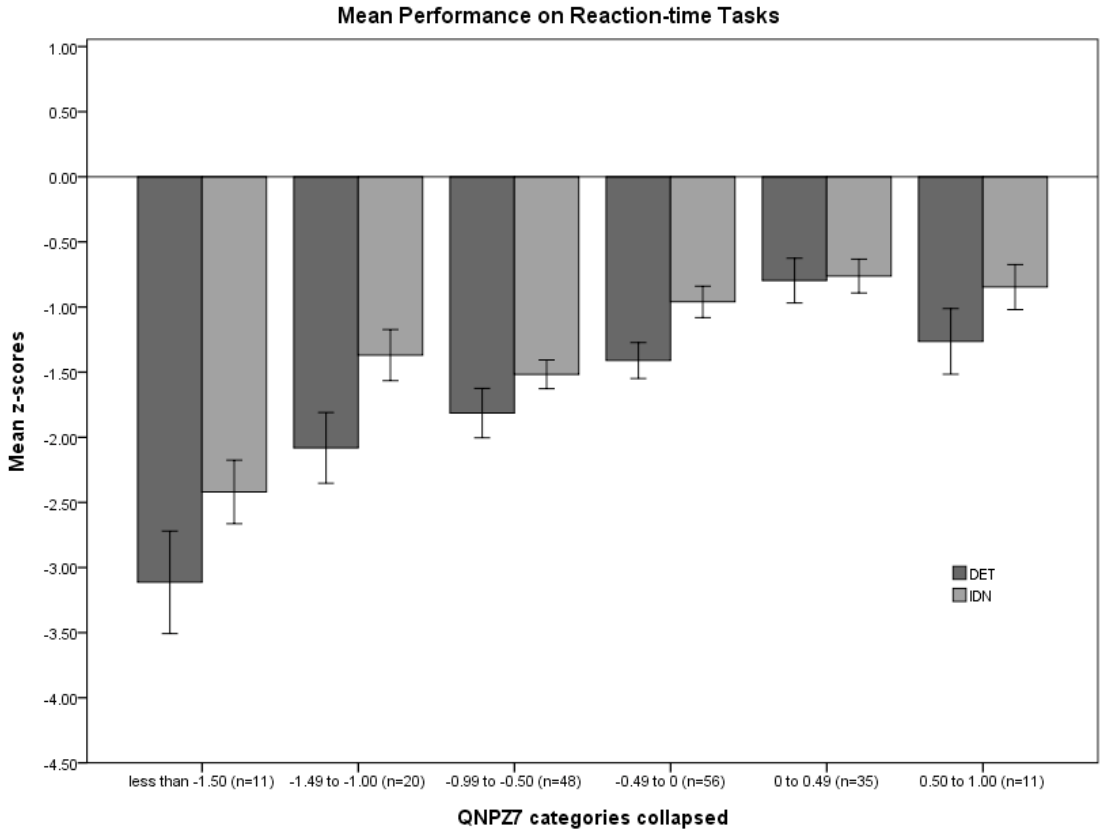


Figure 4a: Average CogState performance on Detection (DET) and Identification (IDN) tasks by cumulative performance on standard neuropsychological battery. Participants performing less than 1.5 SD below the mean on the standard battery are also performing at least 2.5 SD below the mean on Detection and Identification. However, participants performing above the mean on the standard battery are performing, on average, below the mean on CogState. Error bars denote standard error of CogState performance.

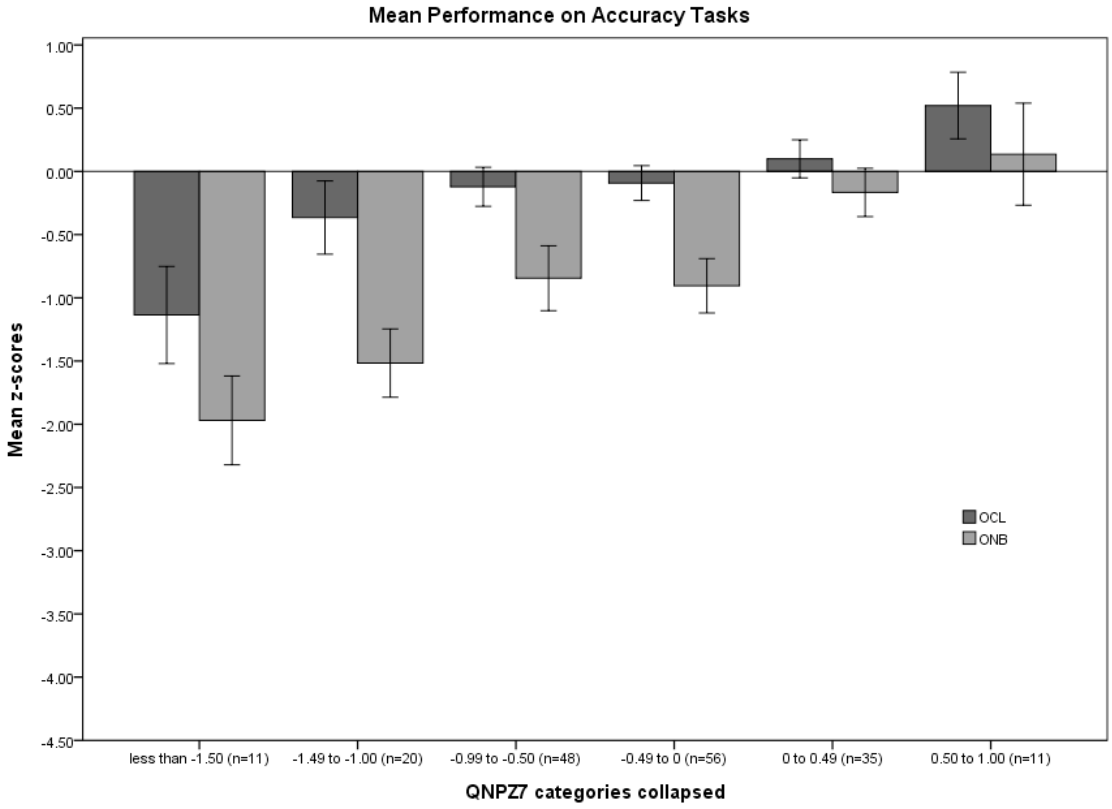


Figure 4b: Average CogState performance on One-Card Learning (OCL) and One-Back (ONB) tasks by cumulative performance on standard neurological battery. Participants performing less than 2 SD below the mean on the standard battery are also performing at least 2.5 SD below the mean on One-Card Learning and One-Back. However, participants performing above the mean on the standard battery are also performing at or above the mean on these tasks in CogState. Error bars denote standard error of CogState performance.

Sensitivity and Specificity Analysis

To investigate other cut-offs that produce the highest sensitivity and specificity for CogState, we tried various combinations described in Table 4. Although various other cut-offs demonstrated higher sensitivity than using the baseline standard (performance of 1 SD below the mean on 2 or more tests), this criterion demonstrated the highest c-statistic (equivalently, area under the receiver operating characteristic (ROC) curve) compared with the gold standard.

Table 4: Sensitivity and Specificity of CogState using varying cut-offs

Cut-offs (SD below the mean on specified number of tasks)	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	c-Statistic
0.75 SD on 1 or more tasks	96 (91-99)	14 (6-27)	74 (67-80)	58 (29-84)	0.549
0.75 SD on 2 or more tasks	75 (66-82)	47 (33-61)	78 (70-85)	42 (29-56)	0.608
0.75 SD on 3 or more tasks	48 (40-57)	76 (62-87)	84 (73-91)	37 (28-47)	0.625
1.00 SD on 1 or more tasks	89 (82-94)	22 (12-36)	75 (67-81)	44 (25-65)	0.564
1.00 SD on 2 or more tasks	65 (56-73)	63 (48-73)	79 (70-86)	48 (37-60)	0.641
1.00 SD on 2 or more tasks	32 (25-41)	88 (75-95)	88 (74-74)	33 (26-42)	0.603
1.50 SD on 1 or more tasks	73 (64-80)	43 (30-58)	77 (68-84)	39 (26-52)	0.581
1.50 SD on 1 or more tasks	45 (37-54)	76 (62-87)	83 (72-91)	35 (27-45)	0.609
2.00 SD on 1 or more tasks	55 (46-63)	63 (48-76)	79 (69-87)	35 (26-46)	0.587
2.00 SD on 2 or more tasks	30 (22-39)	92 (80-97)	91 (77-97)	34 (26-43)	0.611
1 SD on 2 or more tasks OR 2 SD on 1 or more tasks	71 (62-78)	53 (39-67)	79 (71-86)	42 (30-54)	0.619

5 DISCUSSION

Even with full viral suppression, antiretroviral therapy does not fully restore health; thus, increased access to treatment brings with it not only longer lifespans, but also emerging clinical challenges. Key among these challenges are neurocognitive disorders [2]. But existing cognitive assessments, especially in resource-limited settings, are not feasible to integrate into the routine management of HIV. In this study, we investigated a tool, CogState, that had not been used before in sub-Saharan Africa with HIV-positive, adult populations. We found that performance on CogState correlated adequately with performance on the standard battery.

The standard neuropsychological battery is considered the gold standard for determining cognitive impairment [14, 16, 17]. However, because this exam requires trained professionals, extensive testing equipment, and is time consuming, it is not feasible to implement in an urban HIV clinic in Uganda or in similar high-volume settings in sub-Saharan Africa. The IHDS has been previously validated in Uganda and had been shown to be a quick screen for impairment [11]. However, while the IHDS is a very useful screen, the practice effects have not been validated. Since the test comprises of remembering three specific words and a very distinct motor sequence, it would seem very likely to have strong practice effects with multiple administrations; a problem that also exists with the standard neuropsychological battery [8-10].

Not only is the CogState Brief Battery feasible to administer in the Infectious Disease Clinic, but it may also avoid the problem of practice effects because once the CogState rules are learned, every presentation of a playing card is still a novel challenge that is cognitively demanding [13]. Our findings show that regardless of whether

impairment is classified using the dichotomous definition or the clinical Global Deficit Score, those patients who performed poorly on the standard battery consistently performed poorly on CogState, and those performed well on the standard battery performed well on CogState. Therefore, while CogState might not be as sensitive of an instrument as the standard exam or IHDS, it could be a very useful tool to monitor cognitive function over time.

These results highlight several key points regarding the scope of the problem of NCI among HIV-infected individuals in Uganda (and sub-Saharan Africa more generally). Although 80% of our sample was being treated with antiretroviral therapy, more than one-half of the population was classified as impaired on the gold standard instrument for cognitive impairment. Our study also showed that individuals with cognitive impairment were more likely to be classified in WHO Stage 3 and 4 than those who were not impaired. Therefore, as previous findings have suggested, decline of cognitive function is an important clinical consideration even if a patient is being treated with antiretroviral therapy. If cognitive function is not monitored, although a patient's HIV may be managed, her quality of life may be increasingly compromised.

While our findings suggest the benefits of integrating CogState into routine HIV management, there are limitations to our study. First, there is no Ugandan normative database for CogState performance. In this study, American, age-matched, HIV seronegative controls were used for comparison. A normative database needs to be established in Uganda before CogState can be widely used in this setting. A second limitation was that 10 subjects (6%) were not familiar with playing cards; however, we included these subjects in our analysis in the hopes that it reflected how the population as

a whole would perform on CogState. A third limitation is that CogState was not translated into Luganda or any other language commonly spoken in Kampala. Although English is the national language of Uganda, some patients may have benefited from reading and listening to instructions in a different language. In addition, patients who speak English (almost always as a secondary language in this setting) may have systematically greater cognitive reserve than unilingual patients [26]. Finally, because these data are cross-sectional, future studies that focus on how individual performance changes over time are necessary.

In conclusion, we found that performance on CogState correlates usefully with performance on the gold standard neuropsychological exam, especially when using the specific classifications of performing 1 standard deviation below the mean on 2 or more tasks. Thus, despite some limitations, these findings strongly suggest that CogState can serve as a useful and appropriate instrument for the assessment and monitoring of cognitive function among HIV-positive individuals in Uganda and throughout sub-Saharan Africa.

6 APPENDIX A

6.1 Informed Consent

Form
M0345

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Assessing Neurocognitive Impairment in HIV-positive Patients

Sites of Research:
Infectious Disease Clinic, Mulago Hospital, Kampala, Uganda

1a. What you should know about research studies :

- You are being asked to take part in this research study because you are HIV-positive.
- Research studies include only people who choose to take part.
- This consent form explains the research study
- Please read this form carefully and ask questions about anything you do not understand.
- If you do not have questions now, you may ask later.
- If this study relates to a health problem you have, we will explain what other treatment could be given outside the research. You should understand those options before you sign this form.

1b. Why is this research being done?

The purpose of this study is to learn whether a new test using the computer can detect mental problems that result from HIV infection. Normally when a doctor suspects changes in mental abilities, a patient is referred for a full exam, which can take 2 hours or more. This computerized test only takes about 8-10 minutes to complete, and if it proves to be as useful, then it could save both patients and doctors time. No drug treatment is required and no biological samples need be taken for this study. Patients will be interviewed and complete three forms, then complete the computerized test and a set of eight standard exams. Approximately 200 people will take part in this study at the Infectious Disease Clinic at Mulago Hospital

1c. What will happen if you join this study?

If you decide to participate, your thinking will be tested using several simple tasks. Along with these tasks, some questions about your medical history and a series of questions of how well you are able to perform daily activities will also be asked. If you choose to complete these questions, your answers will not be marked as being "good or bad".
This study requires only one visit, and will take less than 2 hours.

2. What are the risks of the study?

The health risks of the study are very small. There is a slight risk of emotional embarrassment in responding to the tests. All procedures will be completed so that your style and feelings are respected. You may refuse to answer any of the questions and you may take rest at any time during the study. You may stop your participation in this study at any time. Every possible measure would be taken to minimize these risks.

3. Are there benefits to being in the study?

If you agree to take part in this study, there may be direct medical benefit to you. The benefits to you from being in this study will include a check-up on your thinking abilities. Any sign or symptom of that

is not normal will lead to an immediate follow-up visit where a doctor will examine you further. This research is also designed to benefit other people who are HIV positive by providing new information.

4a. Will it cost you anything to be in this study?

There will be no cost for you to be in the study.

4b. Will you be paid if you join this study?

You will be paid approximately 10,000 Ugandan Schillings for your participation. Each appointment will be about two hours long.

5. Can you leave the study early?

- You can say you are going to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting your normal medical care.

6. What information is kept private and what information may be given out?

This section tells you what information about you may be used and given out in this study and who may give and receive the information. By signing this consent form, you agree that health information about you may be given out, so long as it does not include information that could identify you.

a. What information about you may be used or given out in this study?
No information that identifies you, such as your name, address, telephone number, or date of birth can be given out. Health information may be given out, but identifying information will NOT be attached to it. Health information would include:

i. Information obtained to see if you can join this study, and any other information that you share with us, including information about your health history and your family health history.
ii. Information obtained during the study, such as how you respond to the study activities or procedures, surveys, and any other medical information we learn from you as a subject in this study.

b. Who may use and give out information about you?
Some people may see your health information and may give out your health information during this study. These include the researcher and the research staff, and other people who need to see the information to help this study or make sure it is being completed properly. However, any identifying information will not be attached to this health information.

c. What if you decide not to give your permission to use and give out your health information?
You do not have to give your permission to use or give out your health information. However, if you do not give permission, you may not participate in this study.

7. What is the role of the IRB?

An Institutional Review Board (IRB) reviews research studies involving human volunteers. The IRB is made up of doctors at Mulago Hospital. The IRB is responsible for protecting a patient's rights.

8. Whom should you call if you have study questions or a study related problem?

If you have questions about this study, you should call the PI, Nirupama Yechoor at 0754408795. For any questions regarding your rights as a participant in this study, contact the chairperson of the School of Medicine Research and Ethics Committee Prof. James Tumwine: Makerere University College of Health Sciences, P.O Box 7072 Kampala, Uganda 1st Floor Clinical Research Building, New Mulago Complex, Mulago Hill Road. Telephone number: +256-414-533541 or the Uganda National Council for Science and Technology. Telephone number: +256-414-250499 or +256-414-250431

9. Do you have to join this study?

You do not have to join this or any research study. If you do join, and later change your mind, you may stop at any time. If you refuse to join or withdraw early from the study, you will not lose any benefits that you would normally get.

10. What does your signature mean?

Your signature below means that you understand the information given to you about the study and in this consent form. If you sign the form it means that you agree to join the study.

WE WILL GIVE YOU A COPY OF THIS CONSENT FORM.

FOR ADULTS CAPABLE OF GIVING CONSENT:

_____

Participant's Signature Date

SIGNATURE (S):

_____

Signature of Person Obtaining Consent Date
(Investigator or IRB Approved Designee)

NOTE: A COPY OF THE SIGNED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR AND A COPY OF THE CONSENT FORM MUST BE PLACED IN THE PATIENT'S RECORD

6.2 Demographics Questionnaire

Demographic Data Forms

1. **Subject ID:**
2. **Examination Date:**
3. **Age:**
4. **Gender:**
5. **First Language Learned:**
6. **Main Language Spoken:**
7. **Are you able to read your main language spoken?**
8. **Are you able to write your main language spoken?**
9. **Education Level:**
10. **Monthly income (household):**
11. **Handedness:** Right ☐ Left ☐

12. **Ethnicity**:

MEDICAL HISTORY

HIV Status

CD4 Count: _____

Viral Load: _____

N0-0, YES-1

13. **Diabetes Mellitus:**
14. **Hypertension:**
15. **Syphilis:**
16. **Head Trauma** (with loss of consciousness of > 1 hour)
17. **If YES for question 17, how many times?**
18. **Stroke:**
19. **Neuropathy:**

    19a.Numbness (negative symptoms)

    19b. Pain, paresthesia (positive symptoms)

20. **Hepatitis**
21. **If yes, 20a) hepatitis A**

20b) hepatitis B

20c) hepatitis C

22. Asthma requiring steroids

23. Any current drug medications:

24. If 23 is YES, specify

25. Prior neurotoxic drug use

24a) Isoniazid

24b) Dapsone

24c) Metronidazole

25. Alcohol Use-CAGE QUESTIONNAIRE No=0, Yes=1

25a. Have you used alcohol in the last 30 days?

25b. How many days a month?

25c. How many beers per day?

25d. How many shots of liquor per Day?

25e. How many servings of wine per day?

25f. Have you ever tried to cut down on the amount of alcohol you take?

25g. Do you become angry when people comment on your drinking?

25h. Do you ever feel guilty about your drinking?

25i. Do you take a morning drink in order for you to function?

OVERALL FUNCTIONAL STATUS

26. Potential work status (job, household, school, etc., as judged by the clinician)**:**

0 – full time, normal work

1 – full time but less demanding

2 - > ½ time

3 - < ½ time

4 – unable to work

5 – temporarily unable to work (if >6 weeks, score as 45)

9 – not obtained

26a. If work capacity is limited (1-6 above), what is the main reason?

0 – not applicable, able to work

1 – neurological disease of some type (CNS, PNS)

2 – systemic medical illness (e.g., pneumonia, cancer)

3 – fatigue

4 – skeletal or other structural restriction

5 – psychological or psychiatric incapacity

9 – uncertain or unknown

27. Fatigue:

0 - none, normal energy and stamina

1 - mild fatigue, limits most demanding activities

2 - moderate fatigue, limits many activities, requires extra rest

3 - severe, major limitation

9 –-uncertain or unknown

UNARC Neurological Symptoms Screen (1-Yes, 0-No) (answered by subject)

28. Have you had any problems with your memory, do you forget things that happened recently, (for example, where you put things, appointments?)
28a. If you have had problems with your memory, have these problems worsened over the past 6 months?
29. Do you have difficulty doing activities involving concentration and thinking?
29a. If you have had difficulties doing activities involving concentration and thinking, have these difficulties worsened over the past 6 months?
30. Do you feel sad or depressed?
30a. If you feel sad or depressed, have these depressed feelings worsened over the past 6 months?
31. Do you have any recent onset, troublesome headaches?……..

Modified Total Neuropathy Score

Parameter	0	1	2	3	4
Motor Symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Sensory Symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to Ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows, or functionally disabling

32. Do you have any clumsiness or slowing of your hand movements interfering with daily activity?
32a. If yes, equate to 0-4 of modified Total Neuropathy Score

33. Do you have any numbness, loss of sensation, or tingling in your toes, feet, or fingertips?
33a. If yes, equate to 0-4 of modified Total Neuropathy Score

34. Do you have any balance difficulty or unsteadiness when you walk?

35. Do you have any stiffness in your neck when you bend your head forward and backward?

36. Have you ever had a fit or seizure?

37. Do you have any problem with bladder control?

38. Karnofsky Performance Scale:

Able to carry on normal activity; no special care is needed.	100 = Normal
	090 = Able to carry on normal activity; minor signs or symptoms of disease
	080 = Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	070 = Cares for self, unable to carry on normal activity or to do active work
	060 = Requires occasional assistance but is able to care for most needs
	050 = Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	040 = Disabled, requires special care and assistance
	030 = Severely disabled, hospitalization is indicated although death is not imminent
	020 = Very sick, hospitalization necessary; active support treatment is necessary
	010 = Moribund, fatal processes progressing rapidly
	000 = Dead

International HIV Dementia Scale

Memory-Registration: Give four words to recall (e.g., in English use dog, hat, bean, red; in Uganda use kopo, engatto, doodo, myufo)

42. Motor-Speed: Have the patient tap the first two fingers of the **non-dominant hand** as wide and as quickly as possible

4 = >15 in 5 seconds
3 = 11-14 in 5 seconds
2 = 7-10 in 5 seconds
1 = 3-6 in 5 seconds
0 = 0-2 in 5 seconds
Score**:**

43. Psychomotor Speed: Have the patient perform the following movements with the **non-dominant hand** as quickly as possible. Demonstrate and have the patient perform twice for practice.

1. Clench the hand in fist on flat surface
2. Put hand flat on surface with the palm down

3. Put hand perpendicular on flat surface on the side of the 5th digit

4 = 4 sequences in 10 seconds
3 = 3 sequences in 10 seconds
2 = 2 sequences in 10 seconds
1 = 1 sequence in 10 seconds
0 = unable to perform
Score**:**

44. <u>Memory-Recall</u>: Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red)

Give 1 point for each word spontaneously recalled
Give 0.5 points for each correct answer after prompting
Maximum = 4 points
Score**:**

45. **IHDS total score (sum of 42, 43, and 44)**

Scoring for CES-D:

47. CES-D Score = (a + b + c + e + f + g + i + j + k + m + n + o + q + r + s + t) - (d + h + l + p)

For each of the following statements, place a check mark in the column that best describes how often you felt or behaved this way during the past week.	**Rarely or none of the time** **(1)** (Less than 1 day)	**Some or Little of the Time** **(2)** (1-2 Days)	**Occasionally or a Moderate Amount of Time** **(3)** (3-4 Days)	**Most or All of Time** **(4)** (5-7 days)
a. I was bothered by things that usually don't bother me.				
b. I did not feel like eating, my appetite was poor.				
c. I felt that I could not shake off the blues even with the help from my friends or family.				
d. I felt that I was just as good as other people.				
e. I had trouble keeping my mind on what I was doing.				
f. I felt depressed.				
g. I felt that everything I did was an effort.				
h. I felt hopeful about the future.				
i. I thought my life had been a failure.				
j. I felt fearful.				
k. My sleep was restless.				
l. I was happy.				
m. I talked less than usual.				
n. I felt lonely.				

o. People were unfriendly.				
p. I enjoyed life.				
q. I had a crying spell.				
r. I felt sad.				
s. I felt that people disliked me.				
t. I could not get "going."				

6.3 Activities of Daily Living

Subject ID:_____
Date:_____

ACTIVITIES OF DAILY LIVING

INSTRUCTIONS TO PARTICIPANT: We are interested in knowing how well you are able to perform common tasks.

- Please circle the number under the "NOW" column that most accurately indicates your current ability level.
- Then circle the number under the "BEST" column that most accurately indicates your highest ability level (this would be the time in your life when you were functioning at your best).

Please add any comments that you feel will help clarify your responses (e.g., when you started having difficulties and what you think are the causes of the problem).

1. Housekeeping	**NOW**	**Best**
I maintain my house/apartment by myself or only need occasional help for larger jobs	0	0
I only perform light daily tasks (wash dishes, make bed)	1	1
I perform some light tasks, but have difficulty keeping my place clean	2	2
I need help with all housekeeping tasks	3	3
I am fully able to do housekeeping, but choose not to do so	8	8

Comments_____

_____

2. Managing finances	**Now**	**Best**
I manage all of my finances (check cashing, banking, handling money) by myself	0	0
I manage routine small purchases, but need help with banking, checking and balancing accounts	1	1
I am not able to handle money accurately	2	2
I am able to handle my own finances, but someone else does them for me	8	8

Comments_____

_____

3. Buying Groceries	**Now**	**Best**
I create my own grocery list and do my own shopping	0	0
I need occasional assistance in buying groceries	1	1
I need someone else to do my grocery shopping for me	2	2
I am able to create my own grocery list and do my own shopping, but someone else does it for me	8	8

Comments_____

_____

4. Cooking	**Now**	**Best**
I plan, prepare, and serve many of my own meals	0	0
I prepare meals if someone else provides me with the right ingredients	1	1
I heat and serve meals provided by others	2	2
I need to have meals prepared and served to me	3	3
I am able to plan, prepare, and serve my own meals but someone else does it for me	8	8

Comments_____

_____

5. Planning social activities	Now	Best
I frequently initiate and plan social activities (e.g., going out, having a party)	1	1
I rarely initiate and plan social activities	2	2
I do not plan and initiate social activities	3	3

Comments_____

6. Understanding reading materials/TV	Now	Best
I understand reading materials (e.g., novels, newspaper) and TV (plots, etc.) without difficulty	0	0
I have occasional difficulty understanding reading materials or TV	1	1
I have frequent difficulty understanding reading materials or TV	2	2
I am unable to understand reading materials or TV	3	3

Comments_____

7. Transportation	Now	Best
I drive my own car or take public transportation on my own (if you do not own a car)	0	0
I arrange my own travel using taxis, but do not drive or use public transportation	1	1
I can travel on public transportation or use taxis if I am assisted by another	2	2
I do not travel at all	3	3

Comments_____

8. Using the telephone	Now	Best
I handle using the telephone without difficulty (looking up and dialing new numbers, etc.)	0	0
I only dial a few well-known numbers	1	1
I answer the telephone, but do not dial	2	2
I do not use the telephone at all	3	3
I do not have access to a telephone	8	8

9. Home repairs	Now	Best
I handle most minor home repairs (plumbing, gardening)	0	0
I need assistance with most minor home repairs	1	1
I am unable to do most repairs by myself	2	2
I am capable of making minor repairs but choose not to	8	8

Comments_____

10. Bathing	Now	Best
I handle all of my bathing needs by myself	0	0
I need occasional assistance with bathing (getting in and out of the tub/shower, etc.)	1	1
I always need help from others when bathing	2	2

Comments_____

11. Dressing	Now	Best
I am able to dress myself and pick out my own clothes	0	0
I dress myself, but someone else must pick out my clothes for me	1	1
I need occasional assistance getting dressed or frequently make mistakes in choosing clothes	2	2
I need frequent assistance in getting dressed	3	3

Comments_____

18. What do you think are your major areas of difficulty at this time?

_____

_____

_____

19. I feel that the difficulties that I am having on the above tasks, if any, are due to: **Now**

Primarily cognitive problems (e.g., thinking, memory, paying attention) 1
Primarily physical problems (e.g., fatigue, feeling sick) 2
Equally cognitive and physical problems 3
I am not having any difficulties on the previous tasks..... 8

Comments_____

_____

20. If you are having more difficulty than you used to with the above tasks, approximately when did the difficulties begin?

Within the last month 1
1 to 6 months ago 2
6 months to 2 years ago 3
2 to 5 years ago 4
More than 5 years ago..... 5
I am not having any difficulties..... 8

12. Shopping (e.g., clothes, other non-food goods)	Now	Best
I take care of all of my shopping needs	0	0
I only make small purchases	1	1
I need someone to go with me on any shopping trip	2	2
I am unable to shop	3	3
I am able to shop, but choose to have someone else do my shopping for me	8	8

Comments_____

13. Laundry	Now	Best
I do all of my own laundry	0	0
I need occasional help in doing the laundry	1	1
I launder only small items (e.g., rinse socks, stockings, etc.)	2	2
All laundry must be done by others	3	3
I am able to do my own laundry, but choose to have others do it for me	8	8

Comments_____

14. Taking/keeping track of medication	Now	Best
I take sole responsibility for taking medications in correct dosages at the correct time	0	0
I take medications that are prepared in individual doses by someone else	1	1
I am unable to track my own medications	2	2
I am able to take care of my own medications, but choose to have someone else do it for me	8	8

Comments_____

15. Child Care	Now	Best
I am fully able to handle child care	0	0
I need occasional assistance in caring for my children	1	1
I need constant assistance in caring for my children	2	2
I do not have children	8	8

Comments_____

16. Work	Now	Best
I am efficient at work	0	0
I am not very efficient at work and have difficulty maintaining attention or finishing tasks	1	1
I am having a great deal of difficulty in maintaining attention or finishing tasks at work	2	2
I am no longer able to work	8	8

Comments_____

17. Please tell us of any other areas in which you are having difficulty:

_____

_____

_____

18. What do you think are your major areas of difficulty at this time?

_____

_____

_____

19. I feel that the difficulties that I am having on the above tasks, if any, are due to: **Now**

Primarily cognitive problems (e.g., thinking, memory, paying attention) 1
Primarily physical problems (e.g., fatigue, feeling sick) 2
Equally cognitive and physical problems 3
I am not having any difficulties on the previous tasks..... 8

Comments_____

_____

20. If you are having more difficulty than you used to with the above tasks, approximately when did the difficulties begin?

Within the last month 1
1 to 6 months ago 2
6 months to 2 years ago 3
2 to 5 years ago 4
More than 5 years ago..... 5
I am not having any difficulties..... 8

6.4 Bolton Functional Assessment

Subject ID:_____
Date:_____

Bolton Functional Assessment

Degree of difficulty completing task or activity

0-None

1-Little

2-Moderate

3-A Lot

4-Often Can't Do Task

For Male Participants

Task or Activity	Degree of difficulty completing task or activity score	Cause of Difficulty
1. Personal Hygiene		
2. Farm		
3. Head the Home		
4. Manual Labor		
5. Plan for the Family		
6. Participate in community development activities		
7. Attend Meetings		
8. Socialize		
9. Participate in burial ceremonies		
10. Other		

Subject ID:_____
Date:_____

Degree of difficulty completing task or activity

0-None

1-Little

2-Moderate

3-A Lot

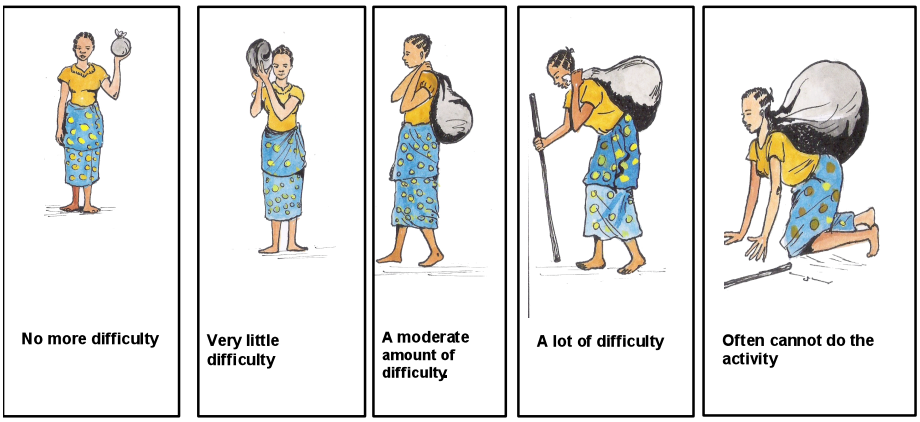
4-Often Can't Do Task

For Female Participants

Task or Activity	Degree of difficulty completing task or activity score	Cause of Difficulty
1. Personal Hygiene		
2. Care for Children		
3. Cook		
4. Wash clothes/utensils		
5. Clean house		
6. Participate in community development activities		
7. Attend Meetings		
8. Grow food		
9. Console and assist the bereaved		
10. Other		

Subject ID:_____
Date:_____

IRC Assessment Instrument:
Nonverbal Response Card for Function*



*Adapted by IRC/Bukavu, Democratic Republic of Congo

7 APPENDIX B

7.1 Standard Neuropsychological Exam

Subject ID:_____
Date:_____

NEUROPSYCHIATRIC AND PSYCHOMOTOR EXAM

1. **WHO/UCLA AUDITORY VERBAL LEARNING TEST**

	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	
Arm						Arm
Cat						Cat
Axe						Axe
Bed						Bed
Plane						Plane
Ear						Ear
Dog						Dog
Hammer						Hammer
Chair						Chair
Car						Car
Eye						Eye
Horse						Horse
Knife						Knife
Clock						Clock
Bike						Bike
Correct:						
Repeat:						
Intrusions:						

Subject ID:_____
Date:_____

	Trial 6			Trial 7
Boot			Arm	
Monkey			Cat	
Bowl			Axe	
Cow			Bed	
Finger			Plane	
Dress			Ear	
Spider			Dog	
Cup			Hammer	
Bee			Chair	
Foot			Car	
Hat			Eye	
Butterfly			Horse	
Kettle			Knife	
Mouse			Clock	
Hand			Bike	
Correct:			Correct:	
Repeat:			Repeat:	
Intrusions:			Intrusions:	

2. **Timed gait (10 yards/9.144 meters)**

TEST SECONDS

1 a. Trial 1:……. ☐

1 b. Trial 2:……. ☐

1 c. Trial 3:……. ☐

2

Subject ID:_____
Date:_____

1 d. If not completed, indicate reason why:…….…

…….……..

3. Digit Span

Trial	Digits Forwards		Digits Backwards	
1	9-7	2	6-2	2
2	4-1	2	1-9	2
1	5-8-2	3	2-8-3	3
2	6-9-4	3	4-1-5	3
1	6-4-3-9	4	3-2-7-9	4
2	7-2-8-6	4	4-9-6-8	4
1	4-2-7-3-1	5	1-5-2-8-6	5
2	7-5-8-3-6	5	6-1-8-4-3	5
1	6-1-9-4-7-3	6	5-3-9-4-1-8	6
2	3-9-2-4-8-7	6	7-2-4-8-5-6	6
1	5-9-1-7-4-2-3	7	8-1-2-9-3-6-5	7
2	4-1-7-9-3-8-6	7	4-7-3-9-1-2-8	7
1	5-8-1-9-2-6-4-7	8	9-4-3-7-6-2-5-8	8
2	3-8-2-9-5-1-7-4	8	7-2-8-1-9-6-5-3	8
1	2-7-5-8-6-2-5-8-4	9		
2	7-1-3-9-4-2-5-6-8	9		
	Forward Score	_____	Backward Score	_____

4. Grooved Pegboard – Non-dominant Hand (GPN)(time to complete 25 pegs)

Non-dominant Hand

a. Hand used: (1-Right, 2-Left): ……...
b. Seconds to complete 25 pegs):…… ☐

c. Number of pegs in:……. ☐

d. Number of pegs dropped:…… ☐

e. If not completed, specify reasons:……..

3

Subject ID:_____
Date:_____

……

Grooved Pegboard Dominant Hand

a. Hand used: (1-Right, 2-Left): …….
b. Seconds to complete 25 pegs):……. ☐

c. Number of pegs in:…… ☐

d. Number of pegs dropped:…….. ☐

e. If not completed, specify reasons:……..

……

5. Verbal Fluency (Animal Naming)

1. _____	16. _____
2. _____	17. _____
3. _____	18. _____
4. _____	19. _____
5. _____	20. _____
6. _____	21. _____
7. _____	22. _____
8. _____	23. _____
9. _____	24. _____
10. _____	25. _____
11. _____	26. _____
12. _____	27. _____
13. _____	28. _____
14. _____	29. _____
15. _____	30. _____

Subject ID:_____
Date:_____

Semantic Verbal Fluency	(Animals)	5 a. Total response	___ ___
		5 b. Total Correct	___ ___
		5 c. Total Repetitions	___ ___
		5 d. Total Errors	___ ___

6. Finger Tapping Dominant Hand (FTD)

Scoring: The average number of taps in five 10-second trials.

Stopping Rule: None

Dominant hand: (1-Right, 2-Left)…….. [ ]

TRIALS TAPS

Trial 1: ……. [ ]
Trial 2: …… [ ]
Trial 3: …… [ ]
Trial 4: …… [ ]
Trial 5: …… [ ]

Specify reasons if any one of the trials were not done:…….……..

…….……

Non- Dominant hand: (1-Right, 2-Left)……..

TRIALS TAPS

Trial 1: ……. [ ]
Trial 2: …… [ ]
Trial 3: …… [ ]
Trial 4: …… [ ]
Trial 5: …… [ ]

Specify reasons if any one of the trials were not done:…….……..

Subject ID:_____
Date:_____

……..……

7. Color Trails 1 and 2

	Time	**Number of Errors**
Color Trails 1		
Color Trails 2		

8. WHO/UCLA Delayed Recall

	Trial 8
Arm	
Cat	
Axe	
Bed	
Plane	
Ear	
Dog	
Hammer	
Chair	
Car	
Eye	
Horse	
Knife	
Clock	
Bike	
Correct:	
Repeat:	
Intrusions:	

8 APPENDIX C

8.1 CogState Exam

The CCAT consists of four computerized cognitive tests, derived from theoretical and developmentally sensitive principles. The tasks themselves measure psychomotor function (Processing Speed or Detection task, DET), attention (Attention or Identification task, IDN), learning (Learning or One card learning task, OCL) and working memory (Working Memory or One back task, OBK), and these have been validated widely in adults. For example, prior research has demonstrated the sensitivity of these tests to adult mild traumatic brain injury and concussion [12, 27-30], psychiatric illness including schizophrenia [31, 32], mild cognitive impairment and early Alzheimer's disease [33, 34] [34] and HIV dementia [35]. The test battery has also been used to detect cognitive changes occurring in healthy adults [36], including when treated with the benzodiazepine midazolam [37] and alprazolam [38], the muscarinic agonist scopolamine [39] and the acetylcholinesterase inhibitor donepezil [39]. The reliability and metric properties of the tests in adults have been described [27, 36, 40-43], and adult normative data have been previously published [36, 44].

The CCAT tasks are based on a 'playing-card' paradigm. Within each of the playing-card tasks, participants are shown a picture of a playing card and asked to answer a question about the card. Different tests are created by changing the question. For example, in the Attention task the question 'Is the card red?' elicits a simple binary choice and is equivalent to a choice reaction time test. The question 'Is the card exactly the same as the previous card?' is used in the Working Memory task to produce a 1-back version of the commonly used n-back working memory paradigm. In all tasks, responses are indicated by pressing the K-key for "YES" or D-key for "NO" on a computer keyboard. The simple, game-like nature of the CCAT tasks, combined with the

consistent response mechanism also ensures that these tests are appropriate for use in children.

Prior research has demonstrated that these tests are sensitive to the effects of stimulant medication in children with ADHD [45], and are appropriate for administration to children as young as 5 years of age [46, 47]. The reliability of the tests in pediatric populations has also been described [46, 47]. However the nature and magnitude of changes in performance on the CCAT tasks from early childhood to adulthood have not been described as yet.

9 APPENDIX D

9.1 Budget

Item	Estimated Expense (USD)	Details/Comments
Travel to and from fieldwork destination (please attach actual itinerary, if available)	$2,000	
Visa fees, if any	$50.00	
Local transportation during fieldwork experience	$300	
Room/board during project (including meals)	$1,200	
Required Supplies (subject to approval, please include as much detail as is possible, and add lines if necessary)	$3,000	Will Cover the following: facility fees ($1,500), printing documents fees ($500), securing information fees ($500), subject compensation ($1,000)
Translation/research assistance, if any	$1,000	
Local IRB fees, if any	$600.00	
TOTAL ESTIMATED FOR FIELDWORK:	$8,150	

10 REFERENCES

1. Robertson, K.R., et al., *The prevalence and incidence of neurocognitive impairment in the HAART era.* AIDS, 2007. **21**(14): p. 1915-21.

2. Volberding, P.A. and S.G. Deeks, *Antiretroviral therapy and management of HIV infection.* Lancet, 2010. **376**(9734): p. 49-62.

3. Robertson, K., et al., *Second assessment of NeuroAIDS in Africa.* J Neurovirol, 2008. **14**(2): p. 87-101.

4. Kaharuza, F.M., et al., *Depression and CD4 cell count among persons with HIV infection in Uganda.* AIDS Behav, 2006. **10**(4 Suppl): p. S105-11.

5. Antinori, A., et al., *Updated research nosology for HIV-associated neurocognitive disorders.* Neurology, 2007. **69**(18): p. 1789-99.

6. Lawler, K., et al., *Neurocognitive impairment among HIV-positive individuals in Botswana: a pilot study.* J Int AIDS Soc, 2010. **13**: p. 15.

7. Castelnuovo, B., et al., *Improvement of the patient flow in a large urban clinic with high HIV seroprevalence in Kampala, Uganda.* Int J STD AIDS, 2009. **20**(2): p. 123-4.

8. Bartels, C., et al., *Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing.* BMC Neurosci, 2010. **11**: p. 118.

9. Beglinger, L.J., et al., *Practice effects and the use of alternate forms in serial neuropsychological testing.* Arch Clin Neuropsychol, 2005. **20**(4): p. 517-29.

10. Heilbronner, R.L., et al., *Official position of the American Academy of Clinical Neuropsychology on serial neuropsychological assessments: the utility and challenges of repeat test administrations in clinical and forensic contexts.* Clin Neuropsychol, 2010. **24**(8): p. 1267-78.

11. Sacktor, N.C., et al., *The International HIV Dementia Scale: a new rapid screening test for HIV dementia.* AIDS, 2005. **19**(13): p. 1367-74.

12. Maruff, P., et al., *Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex.* Arch Clin Neuropsychol, 2009. **24**(2): p. 165-78.

13. Hammers, D., et al., *Reliability of repeated cognitive assessment of dementia using a brief computerized battery.* Am J Alzheimers Dis Other Demen, 2011. **26**(4): p. 326-33.

14. Robertson, K.R., et al., *Pattern of neuropsychological performance among HIV positive patients in Uganda.* BMC Neurol, 2007. **7**: p. 8.

15. Maj, M., et al., *WHO Neuropsychiatric AIDS study, cross-sectional phase II. Neuropsychological and neurological findings.* Arch Gen Psychiatry, 1994. **51**(1): p. 51-61.

16. Miller, E.N., et al., *Neuropsychological performance in HIV-1-infected homosexual men: The Multicenter AIDS Cohort Study (MACS).* Neurology, 1990. **40**(2): p. 197-203.

17. Maj, M., et al., *Evaluation of two new neuropsychological tests designed to minimize cultural bias in the assessment of HIV-1 seropositive persons: a WHO study.* Arch Clin Neuropsychol, 1993. **8**(2): p. 123-35.

18. Wechsler, D., *A standardized memory scale for clinical use.* Journal of Psychology: Interdisciplinary and Applied, 1945. **19**: p. 87-95.

19. Dugbartey, A.T., B.D. Townes, and R.K. Mahurin, *Equivalence of the Color Trails Test and Trail Making Test in nonnative English-speakers.* Arch Clin Neuropsychol, 2000. **15**(5): p. 425-31.

20. Reitan, R.M., *Validity of the trail making test as an indicator of organic brain damage.* Perceptual and Motor Skills, 1958. **8**: p. 271-276.

21. Matthews, C.G.K., H., *Instruction manual for the adult neuropsychology test battery.* 1964, Madison, WI: University of Wisconsin Medical School.

22. Reitan, R.M.W., D. , *The Halstead-Reitan neuropsychological test battery*, in *The neuropsychology handbook: Behavioral and clinical perspectives*1986, Springer Publishing Co.: New York, NY. p. 134-160.

23. Carey, C.L., et al., *Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection.* J Clin Exp Neuropsychol, 2004. **26**(3): p. 307-19.

24. Jawaid, A., et al., *Cardiovascular risk factors associated with lower baseline cognitive performance in HIV-positive persons.* Neurology, 2011. **77**(4): p. 406-7; author reply 467.

25. Maruff, P.C., L.; Brew, B. J.; & Watson, M. *Concordance between a computerized battery and neuropsychological tests in detecting cognitive impairment in HIV+ adults.* in *49th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy Meeting*. 2009. San Francisco, CA.

26. Schweizer, T.A., et al., *Bilingualism as a contributor to cognitive reserve: Evidence from brain atrophy in Alzheimer's disease.* Cortex, 2011.

27. Collie, A., et al., *Cognition in the days following concussion: comparison of symptomatic versus asymptomatic athletes.* J Neurol Neurosurg Psychiatry, 2006. **77**(2): p. 241-5.

28. Straume-Naesheim, T.M., et al., *Do minor head impacts in soccer cause concussive injury? A prospective case-control study.* Neurosurgery, 2009. **64**(4): p. 719-25; discussion 725.

29. Makdissi, M., et al., *Natural history of concussion in sport: markers of severity and implications for management.* Am J Sports Med, 2010. **38**(3): p. 464-71.

30. Moriarity, J., et al., *A prospective controlled study of cognitive function during an amateur boxing tournament.* Neurology, 2004. **62**(9): p. 1497-502.

31. Pietrzak, R.H., et al., *A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia.* J Clin Exp Neuropsychol, 2009: p. 1-12.

32. Pietrzak, R.H., et al., *Stability of cognitive impairment in chronic schizophrenia over brief and intermediate re-test intervals.* Hum Psychopharmacol, 2009. **24**(2): p. 113-21.

33. Darby, D., et al., *Mild cognitive impairment can be detected by multiple assessments in a single day.* Neurology, 2002. **59**(7): p. 1042-6.

34. Maruff, P., et al., *Subtle memory decline over 12 months in mild cognitive impairment.* Dement Geriatr Cogn Disord, 2004. **18**(3): p. 342-348.

35. Cysique, L.A., et al., *The assessment of cognitive function in advanced HIV-1 infection and AIDS dementia complex using a new computerised cognitive test battery.* Arch Clin Neuropsychol, 2006. **21**(2): p. 185-94.

36. Fredrickson, J., et al., *Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies.* Neuroepidemiology, 2010. **34**: p. 65-75.

37. Collie, A., et al., *Cognitive testing in early-phase clinical trials: development of a rapid computerized test battery and application in a simulated Phase I study.* Contemp Clin Trials, 2007. **28**(4): p. 391-400.

38. Snyder, P., et al., *A method for determining the magnitude of change across different cognitive functions in clinical trials: the effects of acute administration of two different doses alprazolam.* Hum Psychopharmacol, 2005. **20**(4): p. 263-73.

39. Snyder, P., et al., *Reversal of scopolamine-induced deficits with a single dose of donepezil, an acetylcholinesterase inhibitor.* Alzheimer's & Dementia, 2005. **1**: p. 126-135.

40. Collie, A., et al., *CogSport: Reliability and correlation with conventional cognitive tests used in post-concussion medical examinations.* Clinical Journal of Sport Medicine, 2003. **13**: p. 28-32.

41. Falleti, M.G., et al., *Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals.* J Clin Exp Neuropsychol, 2006. **28**(7): p. 1095-112.

42. Falleti, M.G., et al., *Qualitative similarities in cognitive impairment associated with 24 h of sustained wakefulness and a blood alcohol concentration of 0.05%.* J Sleep Res, 2003. **12**(4): p. 265-74.

43. Maruff, P., et al., *Fatigue-related impairment in the speed, accuracy and variability of psychomotor performance: comparison with blood alcohol levels.* J Sleep Res, 2005. **14**(1): p. 21-7.

44. Straume-Naesheim, T.M., T.E. Andersen, and R. Bahr, *Reproducibility of computer based neuropsychological testing among Norwegian elite football players.* Br J Sports Med, 2005. **39 Suppl 1**: p. i64-9.

45. Mollica, C.M., P. Maruff, and A. Vance, *Development of a statistical approach to classifying treatment response in individual children with ADHD.* Hum Psychopharmacol, 2004. **19**(7): p. 445-56.

46. Betts, J., et al., *The development of sustained attention in children: the effect of age and task load.* Child Neuropsychol, 2006. **12**(3): p. 205-21.

47. Mollica, C.M., et al., *Repeated assessment of cognition in children and the measurement of performance change.* Neuropsychol Dev Cogn C Child Neuropsychol, 2005. **11**(3): p. 303-10.