

Validation of the CAT-Rapid: A smartphone screening tool for HIV-Associated  
Neurocognitive Disorders in South Africa

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**COMPULSORY DECLARATION**

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## Abbreviations

AAN – American academy neurology  
AD – Alzheimer’s dementia  
ADL – Activities of daily living  
ANI – Asymptomatic neurocognitive impairment  
CAMCI – Computer assessment of mild cognitive impairment  
cART – Combination antiretroviral therapy  
CAT-Rapid – Cognitive assessment tool-rapid  
CTT – Color trails test  
CU – Cognitively unimpaired  
HAND – HIV-associated neurocognitive disorder  
HIV-D – HIV-dementia  
HVLT-R – Hopkins verbal learning test-revised  
IADL – Instrumental activities of daily living  
IHDS – International HIV dementia scale  
MCI – Mild cognitive impairment  
MND – Mild neurocognitive disorder  
MoCA – Montreal cognitive assessment  
NCI – Neurocognitive impairment  
NPV – Negative predictive value  
PPV – Positive predictive value  
PM – Prospective memory  
SES – Socioeconomic status

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### **Abstract**

Existing screening tools are not suitable for the detection of HIV-associated neurocognitive disorders (HAND) in South Africa. Study 1 of the current thesis aimed to establish construct validity of a new screening tool, the Cognitive Assessment Tool-Rapid (CAT-Rapid), in a sample of cognitively healthy South African undergraduates ( $n = 122$ ). Study 2 investigated the tool's diagnostic validity in a sample of HIV-positive adult South Africans ( $n = 89$ ). In Study 1 and Study 2, correlational analyses characterizing the associations between CAT-Rapid subtests and analogous standardized neuropsychological tests sought to establish construct validity. In Study 2, ROC curves, and estimates of sensitivity and specificity values, characterized the CAT-Rapid's diagnostic validity. Results from Study 1 demonstrated adequate construct validity for the CAT-Rapid in the cognitively healthy sample. Results from Study 2 did not demonstrate construct validity of the tool in the clinical sample. Regarding diagnostic properties, at the recommended cut-off score  $\leq 10$ , the CAT-Rapid did not demonstrate optimal sensitivity and specificity in the detection of HAND. Future research should investigate how the CAT-Rapid compares to paper-and-pencil screening tests that have demonstrated promising results in studies emerging from the global north.

## **Validation of the CAT-Rapid: A smartphone screening tool for HIV-Associated Neurocognitive Disorders in South Africa**

More than two-thirds of all HIV-infected persons reside in sub-Saharan Africa (Hemelaar, Gouws, Ghys, & Osmanov, 2006; World Health Organization [WHO], 2009). South Africa contains the world's biggest population of individuals living with HIV, at an estimated 5.26 million (Statistics South Africa, 2013). The relatively recent arrival of combination antiretroviral therapy (cART) in South Africa has transformed HIV from a fatal illness into a chronic disease: Individuals now live for many years with the virus, its associated neurocognitive disorders, and subsequent impact on everyday functioning (Joska et al., 2012; Mahungu, Rodger, & Johnson, 2009; McManus et al., 2012). For example, 17% of individuals in an HIV-positive, cART-treated sample drawn from a Cape Town health clinic had mild-to-severe neurocognitive impairment (Ganaseen, Fincham, Smit, Seedat, & Stein, 2008).

This situation makes effective screening of patients for HIV-associated neurocognitive disorders (HAND) a primary healthcare concern in South Africa (Mothobi & Brew, 2012). Perhaps even more importantly, the arrival of cART has resulted in a decreased incidence and prevalence of HIV-associated dementia (HIV-D), the most severe form of HAND (Heaton et al., 2010; McArthur et al., 2003; Simioni et al., 2010). Consequently, the milder forms of HAND (particularly asymptomatic neurocognitive impairment [ANI], but also mild neurocognitive disorder [MND]) are now more prevalent (Heaton et al., 2011; Joska et al., 2012; Sacktor et al., 2002). This situation results in a dire need for screening tools able to detect these milder forms of HAND, and especially ANI. Unfortunately, such sensitive detection is not a property of most current HAND screening tools (Lu, Brew, Siefried, Draper, & Cysique, 2013; Power, Selnes, Grim, & McArthur, 1995; Zipursky et al., 2013).

Such a screening tool should be a crucial component of clinic visits for at least three reasons. First, patients are typically not sensitive to minor changes in cognition, and so will not self-report these (Becker et al., 2011). Second, a positive diagnosis of HAND can interfere with cART adherence, work performance, and driving capability, and can result in increased morbidity (e.g., increased incidence of more severe forms of HAND) and increased mortality (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; Hinkin et al., 2004; Marcotte et al., 1999, 2004; Stern et al., 2001; Wilkie et al., 1998). Third, in at least some cases, HAND is treatable through appropriate administration of medication regimes. Studies have confirmed improvement due to cART in the cognitive domains of

verbal fluency, executive functioning, attention, and motor speed (Joska et al., 2012; Sacktor et al., 1996, 2000).

### **Neuropathology of HIV**

HIV attacks subcortical brain structures such as the striatum, as well as medial temporal lobe (MTL) structures such as the hippocampus (Cherner et al., 2007; Fujimura et al., 1997). The striatum is part of the striato-pallido-thalamic loop. This loop receives and synthesizes information from various brain regions, then sends that information for further processing in distributed cortical regions. The loop is involved in emotional and cognitive processing; hence, reduced activity in this network is associated with disorders such as schizophrenia and depression (Beblo, Wallech, & Herrmann, 1999; Swerdlow & Koob, 1987).

The basal ganglia are one component of the striatum, and are heavily involved in motor control. Hence, damage to the basal ganglia results in impaired movement and coordination; Parkinson's disease and Huntington's disease are disorders associated with basal ganglia dysfunction (DeLong, 1990; Marsden, 1982).

The MTL structure most notably affected by HIV is the hippocampus. This structure is involved in the processes of episodic memory encoding and consolidation (Squire, 1992; Treves & Rolls, 1994). Damage to the hippocampus and surrounding structures often results in anterograde amnesia (Henke, Buck, Weber, & Wieser, 1997; Tulving & Markowitsch, 1998).

Damage to the structures and neural circuits mentioned above results in a variety of cognitive deficits, all of which are characteristic of the neuropsychological profile of HAND (Cherner et al., 2007; Fujimura et al., 1997; Navia, Cho, Petito, & Price, 1986). Before summarizing that profile, I will (a) discuss the neuropathological variations between the HIV clade B and C subtypes, and (b) describe the diagnostic criteria used to differentiate the various forms of HAND.

### **Neuropathological Differences in HIV Clades**

In South Africa, clade C of the HIV-1 type of the virus is most prevalent (Osmanov et al., 2002; Smith, Kuiken, & Korber, 2003; Van Harmelen et al., 1999). In contrast, clade B predominates in regions (North and Central America, Western and Central Europe, and Australia) from which most research on the neurocognitive outcomes of HIV infection has emerged. Because the different clades might possess different biological characteristics,

(CNS) system vulnerability to each, and the pattern of neurocognitive impairment associated with each, might be different (Paul, Sacktor, Cysique, Brew, & Valcour, 2009; Rao et al., 2008; Tyor, Fritz-French, & Nath, 2013).

There are, however, few studies describing precisely what the neurocognitive differences between clade B and clade C are; this, despite the fact that clade C accounts for more than 50% of all HIV infections. One study examining such differences emerged recently from Brazil. de Almeida et al. (2013) reported on neurocognitive outcomes in HIV-positive clade B- and clade C-infected individuals (some of whom were on cART, and some of whom were not), in comparison to demographically similar HIV-negative individuals. Results indicated that clade B HIV-positive individuals demonstrated a trend towards higher rates of neurocognitive impairment in comparison to clade C HIV-positive individuals.

Apart from variations in the neurocognitive profiles of clade B versus clade C HIV-1 subtypes, a recent study (Rao et al., 2013) that used both *in vitro* and mouse models to investigate HIV gene sequences suggested that, even within clade C, there might be regional differences (e.g., differences between the virus as it manifests in South Africa versus the way it manifests in Southeast Asia) in neurovirulence. More specifically, the mouse model demonstrated greater cognitive impairment in South African clade C HIV-1 in comparison to Southeast Asian clade C HIV-1. This finding yields evidence for the possibility that the South African clade C HIV-1 subtype is more neurovirulent than its Southeast Asian counterpart.

Furthermore, these neuropathological differences might contribute to variability in the neuropsychological signature of HIV within the different clade subtypes. de Almeida et al. (2013) presented one example of such variability. This variability was further confirmed by earlier studies showing a lower prevalence of cognitive impairment in clade C HAND than in clade B HAND (Lindl, Marks, Kolson, & Jordan-Sciutto, 2010; Satishchandra et al., 2000; Wadia et al., 2001). This pattern is supported further by mouse and *in vitro* models, which suggest that the neuropathology of clade C is less severe than that of clade B (Campbell, Watkins, Loret, & Spector, 2011; Constantino, Huang, Zhang, Wood, & Zheng, 2011; Gandhi et al., 2009; Mishra, Vetrivel, Siddappa, Ranga, & Seth, 2008; Ranga et al., 2004; Rao et al., 2008; Samikkannu et al., 2011; Siddappa et al., 2006). Due to these neuropathological (and therefore possible neurocognitive) differences within and between various clades, a screening tool that is specific and sensitive to the South African clade C HIV-1 subtype is critical for clinicians in this country. Furthermore, a

classification system describing the various forms of HAND is necessary to understand the degree of severity in neurocognitive impairment. Hence, the next section discusses one such system that is utilized commonly in the HIV neuropsychology literature and in international clinical settings.

### **Classification of HIV-Associated Neurocognitive Disorders (HAND)**

The three forms of HAND, as categorized by an updated version of the American Academy of Neurology's (AAN) classification (Janssen, Cornblath, Epstein, & Foa, 1991), are ANI, MND, and HIV-D (Antinori et al., 2007). ANI is the mildest form of HAND. Characteristics of ANI include deficits (defined by age- and education-adjusted test performance of 1 standard deviation below the mean) in any two cognitive domains. Diagnostic criteria for ANI further specify that these cognitive deficits should not interfere with successful completion of activities of daily living (ADLs), and that impairment must not be the result of delirium, dementia, or any other neurological or medical etiology.

MND is a more severe form of HAND. It features the same diagnostic criteria as ANI, except for the fact that cognitive impairment must interfere with successful completion of ADLs (Antinori et al., 2007).

The most severe form of HAND is HIV-D, which presents with noticeable impairment in multiple cognitive domains. Impairments in the learning of new information, in information processing, and in attentional abilities are characteristic of this form of the disorder. Here, impairment is defined as age- and education-adjusted test performance of 2 or more standard deviations below the mean. These cognitive deficits are associated with severe problems with ADLs. Again, the diagnostic criteria specify that these deficits must not be associated with delirium, dementia, or any other neurological or medical etiology (Antinori et al., 2007).

### **Neuropsychology of HIV**

Neuropsychological assessment of patients with the aim of differentially diagnosing within HAND, or of determining whether HAND is present or not, requires a test battery. This battery must cover, at least, aspects of the cognitive domains of attention and working memory, verbal memory, executive functioning, information processing speed, and motor abilities (Antinori et al., 2007; Grant, 2008; Gupta, Woods, Weber, Dawson, & Grant, 2010; Kim, Miles, Huber, & Feit, 2008; Robertson et al., 2009; Woods,



Moore, Weber, & Grant, 2009). Such coverage is essential because the neuropsychology of HIV follows a distinct pattern across various cognitive domains.

**Information processing speed and psychomotor coordination.** Bradyphrenia (slow information processing speed) and bradykinesia (slowed movement) are typical features of HAND (Reger, Welsh, Razani, Martin, & Boone, 2002). Further, reduced psychomotor coordination<sup>1</sup> is frequently observed in individuals affected by the virus (von Giesen et al., 2004), and is a predictor of (a) morbidity related to depression, HIV-D, AIDS, and (b) mortality (Akena, Musisi, & Kinyanda, 2010; Dunlop et al., 2002; Sacktor et al., 1996). One way to measure psychomotor coordination is by using the Color Trails Test (CTT; D’Elia, Satz, Uchiyama, & White, 1996). Numerous studies have demonstrated that HIV-positive individuals perform significantly more poorly than their HIV-negative counterparts on this test (e.g., Robertson et al., 2007; Yephthomi et al., 2006). Elements of the CTT also assess executive functioning, a broader cognitive domain within which many HIV-positive individuals have deficits.

**Executive functions.** The term “executive functions” covers a variety of cognitive domains, including (within some taxonomies) complex forms of attention, working memory, and generativity (Chan, Shum, Touloupoulou, & Chen, 2008; Elliott, 2003). The most noticeable cognitive domain affected by HIV is complex attention (Grant, 2008; Woods et al., 2009). Complex attention includes sustained and divided attention. Divided attention<sup>2</sup> is used as processing demands from the environment increase, and is especially vulnerable to impairment under time constraints. Impaired working memory (e.g., impairments in the ability to hold and manipulate information mentally; Baddeley, 1992) is also common (Hinkin et al., 2002; Martin et al., 2001; Stout et al., 1995). Furthermore, individuals diagnosed with HAND experience difficulties with verbal fluency (e.g., with generating words to phonemic or semantic cues under time constraints; Grant, 2008; Robertson et al., 2009). Multiple other executive functions, including abstraction, set-shifting, response inhibition, and decision-making, are also impaired in HIV-positive individuals (Kim et al., 2008).

**Learning and memory.** Specific types of learning and memory are susceptible to impairment in HIV. Affected individuals struggle with explicit learning tasks, as they

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<sup>1</sup>*Psychomotor coordination* is an individual’s ability to combine cognitive skills and physical functions to perform a task (e.g., driving a car).

<sup>2</sup>The term *divided attention* is used to describe a situation where an individual performs more than one task simultaneously, through the distribution of attentional resources.

experience difficulties recalling newly-learned information on episodic memory tasks (Grant, 2008; Gupta et al., 2007; Woods et al., 2009; Yephthomi et al., 2006). For example, recalling items on a shopping list, either immediately or after a delay, might be difficult for HAND patients. Poor memory performance on such tasks is also attributable to executive dyscontrol over episodic memory processes such as encoding and retrieval (Woods et al., 2005). On tasks of episodic verbal learning and memory, executive dyscontrol can lead to impairments in free recall, erratic learning over trials, decreased utilization of organizational strategies such as semantic clustering<sup>3</sup> to learn material and to retrieve learned material, and the frequent occurrence of repetition errors (Gongvatana et al., 2007; Peavy et al., 1994; Woods et al., 2005). Hence, HIV-positive individuals perform significantly more poorly than HIV-negative individuals on the learning and delayed recall trials of these tasks (Carey et al., 2004; Maki & Martin-Thormeyer, 2009; Scott et al., 2006; Woods et al., 2005).

Prospective memory (PM) is also particularly susceptible to HIV-related impairment (Gupta et al., 2010). PM requires an individual to remember to perform a future action. Individuals with deficient PM might experience impaired activities of daily living, including poor medication adherence and financial mismanagement (Brandimonte, Einstein, & McDaniel, 1996; Walter & Meier, 2014; Woods, Weinborn, Velnoweth, Rooney, & Bucks, 2012; Zogg, Woods, Saucedo, Wiebe, & Simoni, 2012).

### **HAND Screening Tools**

Assessment tools that aim to screen for HAND effectively must be able to detect impairment in the above-mentioned cognitive domains. Tools should be sensitive to (at least) psychomotor slowing, impaired episodic memory, and impaired executive functioning. Even more crucial is the fact that screening tools must be able to detect and differentiate between the milder forms of HAND (ANI, MND), as these milder forms are more prevalent in the cART era than HIV-D (Cysique et al., 2010; Heaton et al., 2010, 2011; Joska et al., 2010, 2012; McArthur et al., 2003; Sacktor et al., 2002; Simioni et al., 2010; Zipurksy et al., 2013). As a result, early and accurate detection of the milder forms of HAND by screening tools is also crucial in order to reduce the number of individuals

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<sup>3</sup>The term *semantic clustering* refers to an organizational strategy associated with more efficient encoding and subsequent improved retrieval. Hence, effective use of such an organizational strategy improves performance on verbal learning and memory tasks (Gsottschneider et al., 2011; Murji et al., 2003).

whose HAND status might advance to HIV-D<sup>4</sup> (Kamminga, Cysique, Lu, Batchelor, & Brew, 2013).

Screening tools are an important aid to health practitioners, who need to identify specific cognitive alterations before patients start noticing major behavioral disturbances (Becker et al., 2011). Such screening tools need to be brief (Joska et al., 2011), to allow practitioners to test many patients in a short period. They also need to be user-friendly, so that they can be employed by any healthcare professional (e.g., a nurse), or by a trained technician (Becker et al., 2011). South Africa has a shortage of trained neuropsychologists; therefore, easily administrable tools cater to the lack of such professionals.

Most importantly, screening tools need to be psychometrically sound, specifically in terms of their validity for use in the particular context in which they are to be employed (Manly, Jacobs, & Ferraro, 2002; Nell, 1999). This point is extremely important when applied to a multi-lingual and multi-cultural country, such as South Africa. A large literature emphasizes the importance of neuropsychological assessment tools accounting for the effects of language of administration and culture of the test-taker (Gasquoine, 1999; Hedden et al., 2002; Puente, Perez-Garcia, Vilar-Lopez, Hidalgo-Ruzzante, & Fasfous, 2013; Rosselli & Ardila, 2003). For instance, a recent international study conducted on Spanish-speaking individuals from various cultural backgrounds (participants were from Chile, the Dominican Republic, Puerto Rico, and Spain) showed that neuropsychological test performance differed across cultural subgroups, despite the fact that they spoke the same language (Buré-Reyes et al., 2013). In South Africa, Blumenau and Broom (2011) attributed steeper learning curves and better recall performance on a commonly-used verbal learning test to their linguistic adaptation (e.g., replacing words like *plane* with *taxi* and *butterfly* with *cow*) of this test. However, such an interpretation warrants caution, as the authors did not provide empirical evidence to support their claim that the words used on their adapted version are more culturally appropriate. Nonetheless, such a study draws attention to the need for culturally suitable and valid screening tools designed specifically for use in South Africa.

Construct validity (the extent to which a test accurately measures what it is designed to measure; Cronbach & Meehl, 1955) is an important psychometric element of all assessment tools, including HAND screeners. If a screening tool does not accurately measure the cognitive domain(s) that it purports or intends to, then the robustness of other

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<sup>4</sup>One must note here, however, that not all individuals diagnosed with ANI or MND will eventually be diagnosed with HIV-D (Cysique, Bain, Lane, & Brew, 2012; McArthur et al., 2003).

important psychometric properties (e.g., diagnostic validity) of the instrument are questionable. Unfortunately, there are little or no data on the construct validity of existing HAND screening tools, and hence there remain important questions about the suitability of these tools. A systemic review of HAND screening tools (Kamminga et al., 2013) found that only 3 of 35 studies reported construct validity data, emphasizing the lack of data regarding the correlation between performance on the specified screening tool with performance on gold-standard neuropsychological tests of particular cognitive functions. Furthermore, the 3 studies that did report such data found only small associations.

Finally, screening tools need to include a measure of performance on instrumental activities of daily living (IADLs), in order to aid the differential diagnosis between ANI and MND. Such measures are lacking in current HAND screening tools (Kamminga et al., 2013).

Globally, numerous screening tools exist to detect cognitive impairment; some of these are designed specifically to detect cognitive impairment due to HIV infection. Some of these screening tools take the form of traditional paper-and-pencil tests, while others use computerized/mobile technology. I discuss four major screening tools below. These tools are reviewed because they (a) are popular and widely used, (b) have demonstrated cross-cultural validity in international settings, and/or (c) show potential to be effective in screening for HAND.

**The Montreal Cognitive Assessment (MoCA).** This paper-and pencil instrument (Nasreddine et al., 2005) takes 10 minutes to complete, and does not require special stimuli or complicated scoring software. Hence, it is affordable and easy to use in clinic settings.

The MoCA was designed in Canada to screen for mild cognitive impairment (MCI), a state of cognitive decline found frequently in the space between normal aging and early-stage Alzheimer's disease (AD). MCI is often (somewhat erroneously) regarded as a precursor to AD or other forms of dementia (Albert et al., 2011; Fisk, Merry, & Rockwood, 2003; Flicker, Ferris, & Reisberg, 1999; Petersen et al., 2014; Petersen & Morris, 2003). Diagnostic criteria for MCI specify a decline in cognitive abilities inconsistent with the patient's age and level of education. The criteria further dictate that this decline should not interfere with ADLs (Petersen et al., 2001; Petersen & Negash, 2008).

The MoCA has strong psychometric properties; its test-retest reliability ( $r = .92$ ) and internal consistency (Cronbach's  $\alpha = .83$ ) are particularly good (Nasreddine et al., 2005). Furthermore, the developers report a sensitivity of 90% in detecting MCI, and

sensitivity of 100% and specificity of 87% for detecting mild AD. With regard to cross-cultural validity, the MoCA has been used successfully to detect MCI in the United States, United Kingdom, and South Korea (Lee et al., 2008; Luis, Keegan, & Mullan, 2008; Smith, Gildeh, & Holmes, 2007).

Given these strong psychometric properties and cross-cultural value, the instrument's brevity and ease of administration/scoring, and the fact that it features items that assess domains specifically affected by HIV (e.g., working memory, attention, and executive functions; Gauthier et al., 2006; Luis, Loewenstein, Acevedo, Barker, & Duara, 2003; Nasreddine et al., 2005; Petersen et al., 2001), it might be a useful screening tool for HAND in South African HIV-positive samples. Of course, because the instrument was not developed specifically to screen for HAND, and was not developed for use in South Africa generally, some examination of its suitability is needed.

**The Computer Assessment of Mild Cognitive Impairment (CAMCI).** This computerized instrument (Saxton et al., 2009) takes 20 minutes to complete. It was designed in the United States as a screening tool specific to HAND (Becker et al., 2011). The CAMCI contains eight tasks covering the domains of attention, working memory, psychomotor speed, executive function (in particular, inhibition), and various forms of learning and memory. It is unique among cognitive screening tools because it includes a virtual-reality shopping trip that assesses prospective memory and recognition memory, as well as recollection of events. Due to the virtual reality test feature, the CAMCI is possibly more ecologically valid than many other similar instruments (e.g., it depicts an everyday activity, whereas other instruments do not).

Health professionals easily administer the CAMCI, and it is easy for patients to use. Because it is computer-administered, it might be beneficial in decreasing patient anxiety arising from the presence of a neuropsychologist as an authoritative test administrator. Regarding psychometric properties, the developers report good test-retest reliability ( $r = .75$ ), and sensitivity of 72% and specificity of 97% in detecting minor cognitive impairment in HIV-positive patients. The developers also report that its positive predictive power (number of patients correctly classified as impaired) is 93%, and that its negative predictive power (number of non-patients correctly classified as unimpaired) is 89% (Becker et al., 2011).

**The International HIV Dementia Scale (IHDS).** This paper-and-pencil instrument (Sacktor et al., 2005) takes 3 minutes to complete. It was developed in the United States as a globally suitable means to screen HIV-positive patients for HIV-D. The

IHDS tests three cognitive domains: motor speed (timed finger-tapping test), psychomotor speed (timed alternating hand sequence test), and memory (recollection of four words in 2 minutes). The developers suggest that this screening tool is beneficial for those who are not yet on medication but who present with symptoms of HIV-D.

For several reasons, the IHDS is ideally suited for administration in resource-limited settings or in low- and middle-income countries. First, it does not require the examinee to have completed a high school education. Second, the only instrumentation required is a stopwatch. Third, it is easily administered by any healthcare professional, and can be completed in a non-clinical setting. Despite these positive attributes, various limitations of the IHDS detract from its encouraging potential to be a HAND screener.

The biggest limitation of the IHDS is its relative insensitivity to milder forms of HAND (Sacktor et al., 2005; Zipursky et al., 2013). In other words, patients screened by the IHDS might show a negative result for HIV-D, but might ultimately be diagnosable with a milder form of cognitive impairment, such as ANI or MND. Furthermore, although the IHDS demonstrates good sensitivity in the detection of HIV-D (80%, Sacktor et al., 2005), evidence of this tool's suboptimal psychometric properties is demonstrated in a meta-analysis that evaluated the utility of the IHDS across four studies: Results indicated a pooled sensitivity of 62% (Zipursky et al., 2013).

**NeuroScreen.** This mobile-based instrument takes 20 minutes to complete (Robbins et al., 2014). It was developed in the United States as a screening tool for HAND. NeuroScreen contains 10 subtests examining the cognitive domains of working memory, executive functioning, processing and motor speed, and learning and memory.

NeuroScreen is particularly suited for administration in resource-limited settings or in low- and middle-income countries for several reasons. First, it eliminates the need for additional materials associated with paper-and-pencil test batteries (e.g., stopwatches, test manuals and stimuli, record forms, and writing utensils), thereby saving on associated costs. Second, because the application automatically administers, scores, and times (where necessary) tests, it eliminates the need for administration by a trained neuropsychologist. Third, because its data are stored on a smartphone or tablet, it is easily portable to clinics (Robbins et al., 2014).

Furthermore, NeuroScreen has demonstrated strong psychometric properties (Robbins et al., 2014). In terms of construct validity, the developers report statistically significant moderate-to-strong associations between the tool's subtests and analogous standardized paper-and-pencil cognitive tests. In terms of the tool's ability to detective

cognitive impairment in HIV-positive individuals, it has a sensitivity of 94% and specificity of 64%, with a positive predictive value of 89% and negative predictive value of 78%. These strong psychometric properties, software that make it suitable for resource-limited settings, and its brevity and automated test administration and scoring, make NeuroScreen appear a useful screening tool for HAND in the South African HIV-positive population.

**Use of these screening tools in South Africa.** Below, I discuss the previous and potential future employment in South Africa of the four screening tools reviewed above.

**IHDS.** This is the only screening tool mentioned above whose diagnostic properties have been examined in South African HIV-positive samples. Singh et al. (2008) reported on a pilot study of 20 HIV-positive individuals. Participants, all of whom had been recruited from an inpatient ward at a hospital in KwaZulu-Natal, were administered the IHDS and a short battery of standardized neuropsychological tests. The battery tested performance in the domains of attention, working memory, visuospatial and motor abilities, and executive functioning. Results from this preliminary study indicated that HIV-positive participants were impaired across cognitive domains. With the recommended cut-off score of  $\leq 10$  (Sacktor et al., 2005), the IHDS demonstrated a sensitivity of 88% and a specificity of 50% in the detection of neurocognitive impairment (NCI), thereby demonstrating promising but limited clinical utility in the South African population.

Singh et al. (2008) report various limitations of their study, particularly stressing the preliminary nature of the research. Other limitations include non-representativeness of their sample (e.g., participants were all physically ill with extremely low CD4 cell counts), and a lack of exploration of confounding variables (e.g., low CD4 cell counts, depression) on the measured outcomes. In light of these limitations, they recommended future researchers use a larger sample size that is more generalizable to the population. They also emphasized the necessity of an IHDS cut-off score that is context-specific. Such a cut-off score is necessary because the South African population, generally, has low education and socioeconomic status (SES) levels, and includes numerous home languages and ethnic backgrounds (Burger, Van der Berg, & Von Fintel, 2012; Spaul, 2013).

To address some of the limitations of the Singh et al. (2008) study, Joska et al. (2011) recruited a sample of HIV-positive ( $n = 96$ ) and HIV-negative ( $n = 94$ ) isiXhosa-speaking individuals from healthcare clinics in the Western Cape. Participants were administered the IHDS and a battery of standardized neuropsychological tests. The battery tested performance in the domains of attention, learning and memory, psychomotor speed,

and executive functioning. Results suggested that the IHDS is not a suitable screening tool for the South African isiXhosa-speaking population for a couple of reasons. First, the IHDS did not demonstrate convergent validity with the neuropsychological test battery. As mentioned previously, a lack of demonstrated construct validity is problematic, as it is indicative of the fact that the instrument is not accurately measuring cognitive domains affected by HIV. If this is the case, then the screening tool cannot be used to diagnose potential HAND patients. Second, using the recommended cut-off score of  $\leq 10$ , the IHDS demonstrated a sensitivity of 45% and specificity of 79% in the detection of HIV-D. This poor sensitivity value is indicative of a relatively high rate of false negatives detected by the screening tool. Again, such a result can be explained by the instrument's lack of convergent validity with the gold-standard battery. Another (perhaps complementary) explanation is the cultural inappropriateness of some IHDS items: A screening tool developed in the United States cannot be assumed to be a good diagnostic tool for use in South Africa, due not only to cross-national cultural, linguistic, socioeconomic, ethnic, and educational differences, but also to the great diversity of the South African population.

These unsatisfactory psychometric results reported by Joska et al. (2011) are accompanied by several limitations of the study. Three primary problems were (a) the relatively small sample size, (b) the lack of demonstrated construct validity of the neuropsychological tests for administration in South Africa, and (c) a statistically significant difference between the HIV-positive and HIV-negative groups with regard to age and education level. Despite these limitations, a culturally-modified IHDS suitable for the South African isiXhosa-speaking population might be useful in this country's clinical context.

**MoCA.** The other paper-and-pencil test reviewed above, the MoCA, might be an ideal tool for HAND detection in South Africa due to its brevity and strong psychometric properties. It is also affordable and easy to administer and score, making it a potentially useful resource for South African clinics. Furthermore, domains assessed by the MoCA are consistent with domains affected by HAND; these common domains include working memory, attention, and executive functioning.

Because of the MoCA's cultural specificity to North America, it would need adaptation for South Africa's diverse population. This adaptation might include taking into account the influence of sociodemographic factors such as language, education (both level and quality), and SES. Once it has been adapted, it can be presented as a useful tool for widespread clinical and research use in this country. Hence, Robbins et al. (2013) tested an



adapted version of the MoCA in an isiXhosa-speaking South African sample of HIV-positive ( $n = 39$ ) and HIV-negative ( $n = 39$ ) individuals. This adapted version was created to cater for the relatively high rates of illiteracy and low levels of education in the South African isiXhosa-speaking population, which has been affected greatly by HIV.

Robbins et al. (2013) presented a detailed analysis exploring the cultural appropriateness of items on the MoCA, and examining whether each item could differentiate between the cognitive performance of HIV-negative and HIV-positive individuals. Overall, the authors suggested that the MoCA is able to differentiate between HIV-positive and HIV-negative cognitive performance in a Black South African isiXhosa-speaking sample. Of note, however, is that both HIV-positive and HIV-negative groups had a mean score below 23 on the modified MoCA. This means the average participant in *both* groups would be classified as impaired if one used the North American cut-off score of  $\leq 25$ . This result is problematic, as it sheds light on the fact that some participants might be classified as impaired on this screening tool *not* because of neuropathological (e.g., HIV infection) causes, but because the screening tool is biased by non-neurological (perhaps cultural) characteristics of these participants.

On a related note, floor effects, representative of possible test bias, were found for both HIV-positive and HIV-negative participants on a few of the items (Robbins et al., 2013). These results indicate that certain test stimuli are not suitable for the South African isiXhosa-speaking HIV-positive population (e.g., test stimuli that feature complicated 3-dimensional drawings). The authors attributed this unsuitability to the lack of early and constant exposure to complicated drawings and a consequent lack of knowledge of how such figures should be drawn. Furthermore, participants struggled to name, for example, a line drawing of a rhinoceros, despite the fact that this animal is commonly seen in the mainstream South African media. One explanation for this is the minimal exposure of these participants to mainstream media, resulting in their lack of knowledge regarding this animal.

Despite the various limitations of their study, Robbins et al. (2013) were the first to (a) examine the cultural appropriateness of the MoCA in a South African HIV-positive sample, (b) provide some insights on modification leading to a more suitable version for this context, and (c) provide a temporary modified version of the MoCA for use in South African clinics.

**CAMCI.** The study detailing the development and psychometric properties of this instrument was limited by a small sample size ( $N = 59$ ) that included only participants over

the age of 60 (Becker et al., 2011). Furthermore, although the CAMCI has a high criterion validity index, this result arose from a sample excluding participants with ANI (Saxton et al., 2009). Hence, it is an open question as to whether the tool is effective at detecting the milder forms of HAND (Kamminga et al., 2013). These factors make the CAMCI, as it stands currently, unsuitable for administration to South Africa's diverse population of HIV-positive individuals. Additionally, similar to the MoCA, the CAMCI does not have normative data that cater for the widely disparate levels of educational attainment and quality, and SES, in South Africa.

Apart from these psychometric limitations, a practical limitation of this instrument is that it requires a computer for administration. This is problematic for HIV-positive South Africans living in, for instance, informal settlements, as clinics in these areas have limited or no access to computers.

**NeuroScreen.** NeuroScreen is the most recently developed of the screening tools reviewed above, and the only one that has made use of mobile technology for HAND screening purposes (Robbins et al., 2014). However, an important limitation of the study detailing its development and psychometric properties is the lack of normative data and a small sample size that was comprised mostly of HIV-positive patients with neurocognitive impairment. Thus, the researchers concluded that they cannot ascertain how HIV-positive individuals without neurocognitive impairment would fare on the test. Given these limitations, NeuroScreen requires a more heterogeneous sample in terms of neurocognitive diagnoses (Robbins et al., 2014), but also normative data that caters specifically for the South African population. Without such data, the cultural appropriateness of this screening tool remains questionable.

### **Summary, Rationale, and Specific Hypotheses**

Sub-Saharan Africa is home to more than two-thirds of the world's HIV-infected population. The widespread availability of cART has resulted in lower mortality rates, but because HIV-positive individuals are now living longer, there is an increased incidence of people living with HAND (Robertson et al., 2009; WHO, 2009). HAND has a specific neuropathological signature, affecting discrete brain structures and neural circuits. Hence, there are specific patterns of impairment for each of the categories within HAND.

Although the screening tools reviewed above (the IHDS, MoCA, CAMCI, and NeuroScreen) are brief and easy to use, none of them were designed with South African HIV-positive individuals as the target population. Hence, there are no appropriately

stratified South African normative data for any of those instruments. Additionally, several items on each of those tests might be culturally biased when administered in South Africa. Furthermore, none of the instruments have established cross-cultural and construct validity for administration in South Africa. Because of the country's high HIV prevalence rate, coupled with an ever-increasing number of people using cART, the need for a psychometrically sound and culturally appropriate screening tool to detect HAND in HIV-positive patients is urgent. Moreover, due to the increased prevalence of the milder forms of HAND (Heaton et al., 2011; Joska et al., 2012; Sacktor et al., 2002), an instrument that can detect ANI and MND is essential. Such a tool could serve as a funnel for HIV-positive patients from low-SES backgrounds and resource-limited settings (e.g., the informal settlements or "townships" of South Africa). Incorporating the administration of a HAND screening tool as part of patients' regular clinic check-ups would then funnel patients by identifying those who score poorly within cognitive domains affected by HIV, and then referring them for further testing. Identifying patients with cognitive impairment is beneficial in order to determine, for instance, how any such impairment might affect work performance and ADLs. A valid screening tool that enables the early detection of HAND could also assist medical aid providers by avoiding long-term exorbitant medical costs associated with progressive HAND and the development of protracted illnesses (e.g., AIDS and its associated opportunistic infections). More specifically, cART medication can be administered to affected individuals in the early stages of the infection. These individuals might then show cognitive improvement due to early detection and treatment access. Overall, an effective screening tool means preventative measures can be taken before the cognitive disorder associated with the disease progresses to a more severe state.

Hence, the primary objective of this study was to validate the Cognitive Assessment Tool-Rapid (CAT-Rapid; Joska, 2013), a screening tool (available in paper-and-pencil and smartphone formats) that assesses cognitive impairment due to HIV. Like the IHDS, MoCA, CAMCI, and NeuroScreen, the CAT-Rapid is brief and easy to use. However, like NeuroScreen, it goes one step further in terms of practicality: Because it is free and downloadable onto smartphones, it is widely available for use in South African clinics; this is an especially important feature, given the increasing permeation of smartphones into all socioeconomic (SES) demographics in South Africa (Swanepoel & Thomas, 2012). Furthermore, like NeuroScreen, because the application is stored on a smartphone, it is compact and easily portable to various clinics in the country, and also eliminates the need for numerous paper copies of neuropsychological test batteries, saving

on associated costs. An especially unique aspect of the CAT-Rapid is that it was developed in South Africa, and therefore is more likely to feature culturally appropriate items than NeuroScreen.

I tested the CAT-Rapid in two separate studies in order to establish construct (Cronbach & Meehl, 1955) and diagnostic (Kidd, 1960) validity. Study 1 investigated construct validity by examining whether CAT-Rapid paper-and-pencil and smartphone scores correlate with standardized paper-and-pencil tests that assess the same domains of cognitive functioning as measured by the screening tool. This study utilized cognitively healthy undergraduate students as participants. Study 2 investigated (a) construct validity of the paper-and-pencil CAT-Rapid, and (b) diagnostic validity of the screening tool in a sample of HIV-positive participants.

Study 1 tested these specific hypotheses:

1. The correlation between performance on the trail making test of the paper-and-pencil CAT-Rapid and performance on an analogous standardized paper-and-pencil neuropsychological test (CTT Part 2) will be significantly different from zero.
2. The correlation between performance on the trail making test of the smartphone CAT-Rapid and performance on an analogous standardized paper-and-pencil neuropsychological test (CTT Part 2) will be significantly different from zero.
3. The correlation between the word recall score on the paper-and-pencil CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test (Hopkins Verbal Learning Test-Revised [HVLT-R; Benedict, Schretlen, Groninger, & Brandt, 1998; Brandt & Benedict, 2001] delayed recall trial) will be significantly different from zero.
4. The correlation between the word recall score on the smartphone CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test (HVLT-R delayed recall trial) will be significantly different from zero.

Study 2 tested this specific hypothesis with regard to construct validity:

5. The correlation between the word recall score on the paper-and-pencil CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test (HVLT-R delayed recall trial) will be significantly different from zero.

Study 2 tested this specific hypothesis with regard to diagnostic validity:

6. Using the recommended cut-off score of  $\leq 10$  (Joska, 2013), the paper-and-pencil CAT-Rapid will display high sensitivity and specificity in differentially diagnosing individuals falling in the following HAND categories from cognitively unimpaired (CU) individuals: (a) all three forms of HAND (ANI, MND, HIV-D); (b) the milder forms of HAND (ANI, MND); (c) symptomatic HAND (MND, HIV-D); and (d) HIV-D.

## **Methods**

### **Design and Setting**

Both studies reported on here used a quantitative, correlational, cross-sectional design with nonrandomized selection criteria. Study 1 addressed Hypotheses 1, 2, 3, and 4 by investigating correlations, in a sample of healthy young adults, between (a) scores on the smartphone CAT-Rapid and those on analogous standardized paper-and-pencil neuropsychological tests, and (b) scores on the paper-and-pencil CAT-Rapid and those on analogous standardized paper-and-pencil neuropsychological tests (i.e., it attempted to establish construct validity in a healthy sample). Study 2 addressed Hypothesis 5 by investigating, in a sample of HIV-positive participants, correlations between scores on the paper-and-pencil CAT-Rapid and those on analogous standardized paper-and-pencil neuropsychological tests (e.g., it attempted to establish construct validity in a clinical sample). Study 2 also addressed Hypothesis 6 by investigating the paper-and-pencil CAT-Rapid's ability to detect the various forms of HAND (i.e., it attempted to establish diagnostic validity in a clinical sample).

Study 1 included two 30-minute testing sessions, with a 1-day break inbetween. Each participant was tested individually. To minimize the effects of administration order on results, half the participants received the paper-and-pencil neuropsychological test battery and the paper-and-pencil version of the CAT-Rapid first, and the other half received the CAT-Rapid smartphone test first. I used random assignment to decide which participants received which administration order. Data were collected in a distraction-free room in the Department of Psychology at the University of Cape Town (UCT).

Study 2's neuropsychological testing session lasted 2-3 hours. Each participant was tested individually. All participants were administered the instruments in this order: paper-and-pencil CAT-Rapid, other brief HAND screening tools, paper-and-pencil

neuropsychological tests. Data were collected in a distraction-free room in the Division of Neuropsychiatry within the UCT Department of Psychiatry and Mental Health.

### **Participants**

**Study 1.** A power analysis suggested that, to achieve power of .80 given an alpha of .05 and a correlation coefficient of  $r = 0.3$ , one would require a sample size of  $N = 84$  (Erdfelder, Faul, & Buchner, 1996). To ensure this minimum standard was met, I recruited 122 undergraduate students using the UCT Department of Psychology's Student Research Participation Program (SRPP).

The following eligibility criteria were applied strictly: (a) Participants were required to be fluent English speakers between the ages of 18 and 25 years; (b) individuals formally diagnosed with a psychiatric illness but not currently on psychiatric medication were eligible for participation; (c) individuals were excluded if they were substance abusers (alcohol and/or illicit drugs), or if they had experienced traumatic brain injury with a loss of consciousness, epileptic seizures, stroke, tumor, haemorrhaging, or any other medical event that might have resulted in neurocognitive impairment; and (d) individuals were excluded if they self-reported an HIV-positive diagnosis. All of these language, age, medical, neurological, and psychiatric variables were controlled for in the study design because each might account for variation in cognitive performance. The aim here, then, was to recruit a sample of cognitively healthy participants.

Information relevant to these eligibility criteria were collected via online self-report. A description of the instrument that collected the information is provided below.

**Study 2.** This study is part of a larger ongoing research program that aims to investigate the validity of various HAND screening tools. The program is a collaboration between UCT's HIV Mental Health Research Unit, in the Division of Neuropsychiatry within the Department of Psychiatry and Mental Health, and Johns Hopkins University's School of Medicine (Baltimore, MD). Therefore, participants in the larger research program were HIV-positive South Africans and North Americans.

A power analysis suggested that a sample size of  $N = 43$  was adequate to achieve a power of .90, given a medium effect size (Cohen's  $d = 0.50$ ) and an alpha of .05 (Erdfelder, Faul, & Buchner, 1996). To ensure this minimum standard was met, I used a sample of 89 HIV-positive participants, who were enrolled in the larger research program between September 2012 and July 2014.

HIV serostatus was predetermined by researchers involved in the larger research program within which this study was nested, using standard serum enzyme-linked immunosorbent assays (ELISA). Participants were categorized as cognitively unimpaired, ANI, MND, or HIV-D, according to the AAN's most recent HAND classifications (Antinori et al., 2007). The HIV-positive participants in this study were recruited from and attended outpatient primary health care clinics in Cape Town and surrounding suburbs and townships. Participants were required to have tested HIV-positive within the last 6-12 months. Representatives of the research team invited HIV-positive clinic patients who were established on cART to participate. Hence, all participants had been on cART for at least 6 months prior to the time of testing.

Regarding sociodemographic characteristics, all participants were Black South African isiXhosa-speaking men and women, aged between 23 and 49 years. The eligibility criteria outlined below, which were consistent with those used in the larger research program, were applied strictly. Participants were required to be able to read and write at a Grade 7 level (e.g., they needed to confirm that they had attended school to this level and/or they needed to demonstrate that they were able to read a newspaper headline and to write their full address). Participants were excluded if they refused to sign the informed consent document or if they were identified (via clinical examination on intake) with an untreated active CNS neurological condition or infection (e.g., HIV-related cryptococcal or tuberculous meningitis). Other exclusion criteria included contra-indication to magnetic resonance imaging (MRI; e.g., claustrophobia, metal implanted inside the body, pregnancy), uncorrected visual impairment and hearing loss, and disability in the upper body that could affect motor performance. Furthermore, individuals who had abused alcohol and/or psychoactive substances during the preceding 3 months, or who had a current uncontrolled medical condition (e.g., epilepsy, diabetes mellitus, hypertension, liver, heart, or kidney problem), were excluded. Participants were also excluded if they had a history of significant head injury resulting in either a loss of consciousness for more than 30 minutes or overnight hospitalization, or if they were diagnosed with a psychiatric illness (e.g., schizophrenia, bipolar disorder) and/or were on psychiatric medication. Representatives of the larger research program gathered information regarding these exclusion criteria via a combination of self-report measures and a neuromedical assessment. For instance, they examined criteria regarding psychiatric status and alcohol abuse using the Center for Epidemiologic Studies Depression scale (CES-D; Radloff,

1977), and the Alcohol Use Disorders Identification Test (AUDIT; Babor, Higgins-Biddle, Saunders, & Monteiro, 2001), respectively.

## **Materials**

All of the materials described below were administered to participants in their home language (i.e., in English [all participants in Study 1] or in isiXhosa [all participants in Study 2]).

**Study 1.** The instruments used were a sociodemographic and medical screening questionnaire, an abbreviated paper-and-pencil neuropsychological test battery, and both smartphone and paper-and-pencil versions of the CAT-Rapid.

***Sociodemographic and medical screening questionnaire.*** This questionnaire was completed online. It gathered information regarding participants' age, sex, race, marital and employment status, SES (viz., monthly household income and Hollingshead Index; Hollingshead, 1975), level of education, and nationality (see Appendix A). It also gathered information regarding the eligibility criteria listed above.

***Short paper-and-pencil neuropsychological test battery.*** This battery included tests measuring verbal fluency, processing speed, visual and verbal attention and working memory, set-shifting, and verbal learning and memory. A verbal fluency measure was included in order to establish English language proficiency among participants. Processing speed and attention and working memory measures were included as these are representative of neuropsychological domains affected by HIV (Chan et al., 2008; Elliott, 2003; Reger et al., 2002).

*Verbal fluency* was measured using the Controlled Oral Word Association Test (COWAT; Benton, Hamsher, & Sivan, 1994). The test-taker is asked to generate as many words to a specific phonemic cue, or within a specific semantic category, as s/he can, within the time limit of 1 minute. The phonemic cues are the letters *F*, *A*, and *S*, and the semantic categories are *fruits and vegetables* and *animals*.

*Processing speed* was measured using the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997) Digit Symbol-Coding subtest. This test presents to the test-taker a page with, at the top, the numbers 1 through 9 labelled in square boxes. Each number is matched to a symbol in a box immediately below it. The rest of the page is filled with a series of numbered boxes with an empty box below each. Test-takers are given 2 minutes to copy as many symbols as possible.



*Visual attention and set-shifting* were measured using the CTT (D'Elia et al., 1996). This test comprises two parts: The stimuli for Part 1 are 25 pink or yellow circles, spread over a sheet of regular-sized paper, and the stimuli for Part 2 are 25 pink circles and 25 yellow circles each numbered 1 through 25, again spread over a sheet of regular-sized paper. In Part 1, which measures visual attention, test-takers are required to connect, by drawing lines, the circles numbered 1 through 25 in ascending order, as fast as they can (the color of the circles in part 1 are irrelevant). In Part 2 of the test, which measures set-shifting, test-takers are required to connect the circles again, in ascending order, as fast as they can. However, this time they have the added task of switching between the pink and yellow circles (e.g., pink 1 - yellow 2 - pink 3 - yellow 4).

*Verbal attention* was measured using the WAIS-III Digit Span Forward subtest. The examiner reads, out loud, a string of random digits, with 1 second between each digit. Test-takers are required to repeat this string of digits verbatim. The length of the string of presented digits starts at two, and increases to nine, until the test-taker reaches his/her limit of performance.

*Verbal working memory* was measured using the WAIS-III Digit Span Backward subtest. Administration of this subtest is similar to Digit Span Forwards; this time, however, the test-taker is required to repeat the string of digits in the reverse order from that presented.

*Verbal learning and memory* was measured using the HVLTR (Benedict et al., 1998; Brandt & Benedict, 2001). This list-learning task is used in both clinical and research settings to examine verbal learning and memory. The to-be-learned list contains 12 words, each belonging to one of three semantic categories. Three learning trials precede a delayed recall trial and a 24-item recognition trial. The latter trial features 12 words from target list and 12 distracters; 6 of the latter are semantically related to words on the target list.

The HVLTR has been used in a variety of cultural settings, including Southern India (Gupta et al., 2007; Yephthomi et al., 2006) and China (Cysique et al., 2007). In South Africa, the version of the HVLTR that was used in this study has been used previously, as part of a comprehensive neuropsychological test battery, to examine the relationship between (a) the Apolipoprotein E genotype and neuropsychological function (Hoare, Westgarth-Taylor, Fouche, Combrinck, et al., 2012) and (b) prospective memory impairment and the structural integrity of white matter tracts (Hoare, Westgarth-Taylor, Fouche, Spottiswoode, et al., 2012) in HIV-positive patients. The HVLTR was modified

for use in those studies by three registered South African neuropsychologists, in consultation with the research team. The modification entailed replacing four items from the original test (all in the semantic category of precious stones: *emerald, sapphire, opal, pearl*) with items deemed more culturally appropriate and more familiar to the participants (all in the semantic category of clothing items: *shoes, pants, blouse, skirt*.)

**CAT-Rapid smartphone screening tool.** The CAT-Rapid (Joska, 2013; version 1.0; size: 385k) is free to download from the Google Play Store, and is functional for Android versions 2.2 and upward.

The first stage of this computerized test requires the examiner to select the test language option (in the current study, either English or isiXhosa). The second stage requires the examiner to ask the test-taker this series of questions related to neuropsychological symptoms associated with HAND: “Compared to your best: *Do you often have problems remembering information?*” (addressing verbal memory functioning); “*Are your hands clumsy, shaky or weak?*” (psychomotor ability); “*Have you found it hard to follow a conversation or story?*” (attention and working memory); “*Do you have trouble doing or planning daily activities?*” (executive functioning, specifically planning). The examiner records the test-taker’s response on the smartphone by selecting either *yes* or *no* on the touchpad interface. S/he then clicks *next* on the touchpad, and proceeds with the actual testing component of the CAT-Rapid.

The third stage of the CAT-Rapid requires the examiner to inform the test-taker that s/he will be given four words (*apple, watch, table, red*) to recall. The examiner reads each word with a 1-second interval inbetween. If the test-taker does not repeat the correct words, the examiner repeats the list and the participant tries again. If s/he is still unable to recall the words after this second attempt, the examiner moves on to the fourth stage of the test. If the participant recalls the words successfully, the examiner informs the test-taker that s/he will be required to repeat the words at a later stage in the testing session.

The fourth stage of the CAT-Rapid addresses visual attention, set-shifting, and processing speed. This stage requires the examiner to read the following instruction to the test-taker: “*In this next test, please draw a line connecting the numbers and letters starting from the lowest number. You must switch between numbers and the letters from start to finish. Don’t lift your finger off the screen. Here is a demonstration.*” The examiner then gives the test-taker a demonstration of how to complete, on the smartphone, a task similar to the Trail Making Test Part B (Reitan, 1955). The test-taker then attempts to perform the

test as quickly and accurately as possible. This subtest is timed by the smartphone application; therefore, a completion time is provided at the end of the test.

The final stage of the CAT-Rapid addresses verbal learning and memory. Administration requires the examiner to ask the test-taker to recall the four words presented earlier. If the test-taker cannot remember the word(s), the examiner gives him/her a semantic cue for each: *fruit* (for apple), *jewellery* (for watch), *furniture* (for table), and *color* (for red). The examiner electronically chooses *yes* if the test-taker recalls the word correctly, *hint* if the test-taker recalls the word correctly given the semantic cue, or *no* if the test-taker does not recall the word at all.

After completion of this final stage of administration, the test-taker's results are displayed on the smartphone's screen. The results are divided into three categories: *symptoms*, *trail making*, and *word recall*. Each category has a possible score out of 4, for a total of 12 possible points. A diagnostic interpretation accompanies the score. The developer's intent is for a score of more than 10 to indicate that a diagnosis of dementia is unlikely (e.g., if symptoms are present, another cause for these should be investigated, or an additional opinion and/or comprehensive neuropsychological assessment should be sought). A score of 10 and below is intended to indicate that dementia might be present. In this case, the diagnosis is confirmed only after (a) the exclusion of other causes for symptoms, (b) the application of clinical judgement, and (c) further neuropsychological testing.

***Paper-and-pencil version of the CAT-Rapid.*** This version of the CAT-Rapid is analogous to the electronic version, presenting the same tests in the same order (see Appendix B). The only difference is that a stopwatch is required for this paper-and-pencil version, in order for the examiner to manually record the completion time of the trail making subtest.

**Study 2.** All of the above-mentioned neuropsychological tests were administered to participants in the clinical sample. However, due to the aims of the larger research project, these tests were administered as part of a comprehensive neuropsychological battery. This battery examined the cognitive domains of motor coordination, executive functioning (e.g., attention, working memory, planning, set-shifting, inhibition, cognitive flexibility, verbal generativity), information processing speed, visuospatial abilities, verbal and visual memory, and general intellectual functioning (IQ).

The comprehensive neuropsychological battery included the following tests, administered in this order: IHDS (Sacktor et al., 2005), Simioni neurocognitive symptoms

questionnaire (Simioni et al., 2010), Center for Epidemiologic Studies Depression scale (CES-D; Radloff, 1977), paper-and-pencil CAT-Rapid (Joska, 2013), Grooved Pegboard Test (Klove, 1963), HVLT-R (Benedict et al., 1998; Brandt & Benedict, 2001), Rey-Osterrieth Complex Figure Test (Lezak, Howieson, Bigler, & Tranel, 2012), Mental Alternation Test (MAT; Jones, Teng, Folstein, & Harrison, 1993), WAIS-III Digit Symbol-Coding subtest (Wechsler, 1997), WAIS-III Digit Span Forwards and Backwards subtests (Wechsler, 1997), CTT (D'Elia et al., 1996), Trail Making Test part B (TMT; Armitage, 1946; Reitan, 1955), Stroop Color and Word Test (SCWT; Stroop, 1935), Wisconsin Card Sorting Test (WCST; Berg, 1948; Grant & Berg, 1948), Controlled Oral Word Association Test (COWAT; Benton et al., 1994), Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), MoCA (Nasreddine et al., 2005), and Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975).

## **Procedure**

**Study 1.** The procedure consisted of a screening phase, test administration and data recording of the paper-and-pencil neuropsychological test battery, and administration and data recording of both versions of the CAT-Rapid. Each component is discussed in detail below.

**Screening phase.** Potential participants received an email providing details about the study (e.g., available appointment times, location of the study, eligibility criteria). The email also informed them that they needed to complete a screening questionnaire online to confirm eligibility. A web link was provided for this screening questionnaire. Finally, the email noted that the researcher would contact those who met eligibility criteria. (The researcher also contacted those who did not meet the criteria, thanking them for their interest in this study, and referring them to an electronic announcement board displaying options for alternative research projects.)

On the specified day and time, the participant arrived at the designated room in the Department of Psychology. The researcher, a female postgraduate student in clinical neuropsychology, greeted and accompanied the participant inside. S/he was then seated at a desk, and asked to read the informed consent document (see Appendix C). The researcher then verbally confirmed the participant's rights, as stated in the informed consent document. If s/he agreed to the terms of the study and signed the form, testing proceeded.

***Neuropsychological test administration.*** The researcher began by explaining the various tests included in the abbreviated paper-and-pencil battery, and then gave participants clear instructions as to how to complete the first test. Appropriate standardized instructions, as well as an opportunity to ask any questions before beginning, were provided before commencement of each test in the battery. Participants completed the neuropsychological tests in this order: verbal fluency, processing speed, visual attention and set-shifting, verbal attention and working memory, and verbal memory. Each of the two testing sessions lasted no longer than 30 minutes.

***Data recording for the neuropsychological tests.*** Regarding the Digit-Symbol Coding subtest, the researcher recorded the total number of correctly completed symbols. Regarding the CTT, the researcher recorded the time it took the participant to complete each part of the test. Lastly, regarding the Digit Span Forward and Backward subtests, the researcher recorded the participant's total score for each, as well as the combined total score, using conventional scoring methods detailed in the test manual (Wechsler, 1997).

***CAT-Rapid smartphone and paper-and-pencil administration.*** Before beginning the smartphone administration, the researcher briefly explained the various tests included in the application. Participants were then provided with the test's standardized instructions. Before commencing each test, participants were allowed to ask any questions. Administration of the paper-and-pencil CAT-Rapid was formally identical to that of the smartphone CAT-Rapid.

***Data recording for the CAT-Rapid.*** Regarding data recording for the smartphone version of the CAT-Rapid, the application automatically recorded scores on each of the subtests. Regarding data recording for the paper-and-pencil version, the researcher recorded information for the three different sections of the test. First, in terms of the symptom questions, the researcher recorded the *yes* or *no* response for each of these, followed by the total symptom question score (out of a maximum total possible score of 4). A response of *yes* resulted in 0 points for the specified question, and a response of *no* resulted in 1 point. Second, in terms of the trail making test, the researcher recorded the time it took the participant to complete the test, in addition to the participant's total score on this item. The total score was calculated in this way: 1 point was designated for each correctly completed sequence (i.e., 1-A, 2-B, 3-C, 4-D), for a maximum total possible score of 4. Third, in terms of the word recall test, the researcher recorded the *yes*, *no*, or *hint* response for each of the four words, followed by the total word recall score (out of a maximum total possible score of 4). A response of *yes* resulted in 1 point if the participant

was able to correctly recall the word unaided; a score of 0.5 was recorded if the participant was able to correctly recall the word when aided by a semantic cue; and a response of *no* resulted in a score of 0 if the participant was not able to correctly recall the word, even with the semantic cue. Finally, the participant's total CAT-Rapid score was recorded (out of a maximum total possible score of 12).

**Debriefing.** At the end of the second testing session, the researcher debriefed each participant completely. Further details regarding this process are described below. The researcher then thanked the participant for his/her time and participation, and escorted him/her from the room.

**Study 2.** One examiner was responsible for test administration. This examiner was a Black, South African, isiXhosa-speaking 36-year-old man. He had 12 years of education, and had received extensive training in the standardized administration of the test battery from clinical psychologists and neuropsychologists employed within UCT's HIV Mental Health Research Unit. At the time of the study, the examiner had been working for approximately 5 years as an HIV Neuropsychology Technician in that Unit.

**Preliminary procedure.** Participants were responsible for their own transport to the study venue. Upon arrival, the participant was greeted by the examiner, and then escorted to the testing room. S/he was then seated at a desk, and asked to read the informed consent document (see Appendixes E and F). The examiner then verbally reiterated the participant's rights, as stated in the informed consent document. If s/he agreed to the terms of the study and signed the informed consent form, the test session proceeded.

**Neuropsychological test administration, and data recording for the neuropsychological tests and paper-and-pencil CAT-Rapid.** These procedures were identical to those described above for Study 1, with these exceptions: (a) the test battery was administered over one session of 2-3 hours; (b) the participant was administered a comprehensive neuropsychological test battery; (c) the participant was administered the paper-and-pencil version of the CAT-Rapid only; (d) to account for cross-language differences in the frequency with which different letters begin words (Ferrett et al., 2014), the phonemic fluency test was administered using the letters *M*, *A*, and *V*, rather than *F*, *A*, and *S*; and (e) data recording for the paper-and-pencil CAT-Rapid trail making test included only the participant's total score on this item; completion time was not recorded.

**Debriefing.** Upon the completion of the test battery administration, participants were not debriefed formally. Further details regarding this process are described below.

Participants were then thanked for their time, remunerated, and escorted from the testing center.

### **Ethical Considerations**

The research described here complies with the guidelines stipulated in the University of Cape Town's Codes for Research involving human subjects. The Human Research Ethics Committee of the University of Cape Town's Faculty of Health Sciences granted ethical approval for the larger research programme within which this research was nested (REC REF: 203/2008; see Appendix G). The Research Ethics Committee of UCT's Department of Psychology granted additional ethical approval for Study 1.

**Informed consent and confidentiality.** In both Study 1 and Study 2, participants completed an informed consent form (in either English or isiXhosa) prior to participation. In Study 2, the isiXhosa version was translated from the original English by the same examiner who administered the neuropsychological test battery. Additionally, in both Study 1 and Study 2, autonomy and respect for individuals was upheld: Participants were told, in the abovementioned documents and by the researcher prior to test administration, that their participation would be voluntary. Participants were also informed that they would be allowed to withdraw from the study at any point without negative consequences. The informed consent document listed the researcher's contact details so that participants could contact her or the principal investigator of the larger research program should any questions and/or concerns have arisen.

Furthermore, in both Study 1 and Study 2, participants were told that all data they provided would be kept confidential and anonymous. To ensure that these conditions held, each participant was assigned a unique study number that was the sole identifying information on all of the study documents. Only the research team had access to the key linking participant names with study numbers. Participants' data were stored in a secure room, either in UCT's Department of Psychology (Study 1), or UCT's HIV Mental Health Research Unit (Study 2).

**Risks.** The procedures of both Study 1 and Study 2 posed minimal risks to participants. No physical, psychological, or social harm were inflicted. The main risk was that participants might grow fatigued throughout the testing session(s); however, they were allowed the opportunity to take small breaks at any point during each session, if need be. They were told that they were not obligated to complete all aspects of the neuropsychological tests; if they wished to skip over a task, they were allowed to do so

with no penalty. In Study 2, particularly, participants might have been at risk of feeling uncomfortable, embarrassed, or shy when asked to discuss possible mental health problems. Furthermore, some participants might have felt that they would rather remain unaware of any neuropsychological impairments they might have. Regarding these risks, participants were informed that they should discuss any of these concerns with a member of the research team who was a qualified neuropsychiatrist, who would address such concerns accordingly.

**Benefits and compensation.** In Study 1, undergraduate students received course credit (2 SRPP points) if they completed both testing sessions. In Study 2, participants benefited in three ways. First, they gave a health interview that allowed a neuropsychiatrist to diagnose and treat any problems that exist. Second, a neuropsychiatrist diagnosed any possible memory and cognitive problems, allowing treatment of these impairments and support with managing participants' HIV/AIDS-related complications. Third, participants received ZAR150.00 to cover their transportation costs to and from the test site.

**Debriefing.** In Study 1, at the end of the second testing session, participants were handed a debriefing document (see Appendix D), and were verbally debriefed by the researcher regarding the purpose of the study. The purpose of this debriefing session was to fully inform participants about the study's purposes, and to ensure that they had not sustained psychological harm by participating. They were told that the study aimed to validate a screening tool developed for South Africa's HIV-positive population. They were also informed about the importance of HAND detection in South Africa, and the researcher explained why the five specific neuropsychological subtests were included in both testing sessions. Participants were allowed to ask any questions, to voice any concerns or comments, and to leave contact details if interested in the results.

In Study 2, there was no formal debriefing procedure. This aspect of the procedure was consistent with that of the larger research program within which the study was nested. However, participants with clinical problems or psychological distress, as detected via verbal communication between the examiner and the participant at the end of the session, were referred to appropriate sources for counselling or assistance.

### **Data Management and Statistical Analyses**

All statistical analyses were conducted using SPSS version 22. The threshold for statistical significance was set at  $\alpha = .05$ , unless indicated otherwise.



For both studies, I calculated descriptive statistics (specifically, measures of central tendency and of variance) for each of the sociodemographic and clinical outcome variables, thus helping describe each sample's characteristics in detail. To further explore the data distributions, I created histograms and stem-and-leaf plots. Furthermore, I calculated Pearson's product-moment correlation coefficients ( $r$ ) for continuous variables, and Spearman's  $\rho$  coefficients for categorical variables, to determine the strength and direction of relationships of interest. I interpreted a correlation of .70 to 1 as large, of .50 to .60 as moderate, and below .40 as small (Field, 2009; Tredoux & Durrheim, 2002).

### **Study 1.**

***Deriving outcome variables.*** Regarding sociodemographic information, the researcher recorded participants' self-reports of age, sex, race, SES (measured by a combination of monthly household income and the Hollingshead Index), and years of education completed. Handedness was also determined by self-report, and was confirmed by the researcher's observations during testing.

Regarding outcome variables for both versions of the CAT-Rapid, the researcher recorded the following for each participant: (a) scores on each of the individual symptom questions and the total symptom question score; (b) score on the trail making test; (c) time to complete the trail making test; (d) score on each word recall question; (e) total word recall score; and (f) total score. Regarding outcome variables for the paper-and-pencil neuropsychological tests, the researcher recorded the following scores for each participant: (a) time to complete the CTT Part 2; (b) total number of words recalled on the HVLT-R delayed recall trial; (c) raw score on the WAIS-III Digit Span Forward test; (4) raw score on the WAIS-III Digit Span Backward test; and (d) raw score on the WAIS-III Digit Symbol Coding subtest.

***Preliminary analyses.*** Before proceeding to hypothesis testing, I conducted a series of additional analyses. First, I conducted a series of paired-sample  $t$ -tests and chi-square analyses for continuous and categorical CAT-Rapid outcome variables respectively, in order to determine whether there were significant between-administration differences in favor of the one version of the CAT-Rapid over the other (i.e., paper-and-pencil versus smartphone). Second, I conducted a series of correlational analyses to investigate whether outcome variables derived from the two different versions of the CAT-Rapid were positively associated. I conducted these analyses to examine whether the two versions of the CAT-Rapid measured cognitive status similarly. These analyses provide insight for

clinical settings, as they answer the question of whether patients will deliver similar results regardless of which version of the instrument is administered to them.

***Inferential statistical analyses.*** Hypothesis 1 stated that the correlation between performance on the trail making test of the paper-and-pencil CAT-Rapid and performance on an analogous standardized paper-and-pencil neuropsychological test will be significantly different from zero. Therefore, the first bivariate correlation of interest was between time to complete (a) the paper-and-pencil CAT-Rapid trail making test and (b) the CTT Part 2.

Hypothesis 2 stated that the correlation between performance on the trail making test of the smartphone CAT-Rapid and performance on an analogous standardized paper-and-pencil neuropsychological test will be significantly different from zero. Therefore, the second bivariate correlation of interest was between the time to complete (a) the smartphone CAT-Rapid trail making test and (b) the CTT Part 2.

Hypothesis 3 stated that the correlation between the word recall score on the paper-and-pencil CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test will be significantly different from zero. Therefore, the third bivariate correlation of interest was between (a) the paper-and-pencil CAT-Rapid word recall score and (b) the HVLTR delayed recall score.

Hypothesis 4 stated that the correlation between the word recall score on the smartphone CAT-Rapid and that on the analogous standardized paper-and-pencil neuropsychological test will be significantly different from zero. Therefore, the fourth bivariate correlation of interest was between (a) the smartphone CAT-Rapid word recall score and (b) the HVLTR delayed recall trial score.

## **Study 2.**

***Deriving outcome variables.*** Regarding sociodemographic information, the examiner recorded participants' self-reports of age, sex, and years of education completed. Handedness was also determined by self-report, and was confirmed by the examiner's observations during testing. Regarding clinical information, the examiner recorded participants' CD4 cell counts from their neurological exam chart.

Regarding outcome variables for the paper-and-pencil version of the CAT-Rapid, the examiner recorded the following for each participant: (a) total word recall score, and (b) total score. Regarding outcome variables for the paper-and-pencil neuropsychological tests, the researcher recorded scores on the HVLTR delayed recall trial.

**Preliminary analyses.** Before proceeding to hypothesis testing, I conducted a series of additional analyses. First, I conducted a series of one-way ANOVAs that sought to detect whether there were significant between-group differences for each of the continuous CAT-Rapid and neuropsychological test outcome variables. For between-group comparisons of categorical variables, I used Fisher's exact tests as the assumption of expected cell frequencies greater than 5 was not upheld. I also conducted a series of 4-step hierarchical multiple regression models that sought to determine the extent to which the CAT-Rapid's symptom questions were significant predictors of total score on the instrument. Such analyses were conducted in order to determine (a) how much of the variance in the CAT-Rapid's total score these symptom questions explain, and (b) which symptom questions explained the most/least of the variance in the instrument's total score.

**Inferential statistical analyses.** Hypothesis 5 stated that the correlation between the word recall score on the paper-and-pencil CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test will be significantly different from zero. Therefore, the bivariate correlation of interest in this study was between (a) the paper-and-pencil CAT Rapid word recall score and (b) the HVLTR delayed recall trial score.

Hypothesis 6 stated that, using the recommended cut-off score of  $\leq 10$  (Joska, 2013), the paper-and-pencil CAT-Rapid will display high sensitivity and specificity in the differential diagnosis between HIV-positive cognitively unimpaired (CU) participants versus those with: (a) all of the three forms of HAND (ANI, MND, HIV-D); (b) the milder forms of HAND (ANI, MND); (c) symptomatic HAND (MND, HIV-D); and (d) HIV-D. Before investigating the diagnostic properties of the screening tool, participants' neurocognitive disorder status was determined using the neuropsychological test battery described earlier, in combination with evaluations of functional assessment. These evaluations, administered to all participants who were part of the larger research program within which this study was nested, included an objective neurological examination, as well as subjective self-report measures. These measures included a combination of visual analogue scales pertaining to cART treatment, the Lawton Activities of Daily Living Scale (Graf, 2009; Lawton & Brody, 1969), and the Karnofsky Performance Scale (Karnofsky & Burchenal, 1949). Results from both the neuropsychological test battery and the functional assessments were used to classify participants as either CU or as ANI, MND, or HIV-D. The final classification was established via consensus after case conferences involving a neuropsychiatrist and neurologist (the former from the South African research team, and

the latter from the Baltimore research team). This procedure was completed for all participants who were part of the larger research program within which this study was nested.

Once all participants had been classified, examination of the diagnostic validity of the CAT-Rapid proceeded across two major steps. First, to achieve an overall sense of the diagnostic capabilities of the tool, I generated receiver operating characteristic (ROC) curves to examine the tool's ability to discriminate between CU participants and those classified within the various HAND categories. SPSS helped generate optimal cut-off scores in .25 increments; these were identified as those that provided the best balance between sensitivity and specificity in terms of the highest achievable diagnostic accuracy.

Second, to describe the diagnostic capabilities of specific cut-off points, I used SPSS to generate 2 x 2 contingency tables. These tables showed the number of true positives, true negatives, false positives, and false negatives of the CAT-Rapid at the specified cut-off point. I then plugged these values into an online diagnostic calculator ([http://www.medcalc.org/calc/diagnostic\\_test.php](http://www.medcalc.org/calc/diagnostic_test.php)), which determined the tool's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the chosen cut-off score. This procedure was applied to the screening tool at the recommended cut-off point of  $\leq 10$  (Joska et al., 2013), and at alternative cut-off points that I explored in order to determine whether one might improve the screening tool's diagnostic properties.

For all comparisons, sensitivity was the proportion of the various HAND participants classified correctly, and specificity was the proportion of CU HIV-positive participants classified correctly (Altman & Bland, 1994; Lalkhen & McCluskey, 2008). The area under the curve (AUC) values, generated from the ROC analyses, explored the classification accuracy of the CAT-Rapid for distinguishing between CU participants and participants within the various HAND categories. Larger AUCs were interpreted as more diagnostically accurate; specifically, AUC values higher than .50 were taken as indicative of the fact that the CAT-Rapid is better than chance at predicting a diagnostic outcome with nominal discriminative ability (Zhou, Obuchowski, & McClish, 2002).

I also conducted a set of secondary analyses that were not related directly to any of the a priori hypotheses. A series of one-way ANOVAs sought to detect whether there were significant between-group differences (i.e., CU versus ANI versus MND versus HIV-D) for each of the continuous sociodemographic and clinical variables (viz., age, highest level of education, CD4 cell count). Such analyses were conducted to examine whether any of

these variables might have exerted a confounding influence on the diagnostic results. For each between-group comparison of a continuous variable, I ensured that the assumptions underlying the parametric statistical test held. For between-group comparisons of the categorical variables (viz., sex, handedness), I used chi-square tests of contingency. Fisher's exact tests were used here, as the assumption of expected cell frequencies greater than 5 was not upheld.

## **Results**

### **Study 1: Construct Validity of the CAT-Rapid in a Cognitively Healthy Sample**

**Sample characteristics.** Table 1 presents a summary of key sociodemographic characteristics of the current student sample. Overall, the sample was aged between 18 and 25 years, had between 12 and 17 years of education, was mostly from an SES of at least 7 on the Hollingshead Index (ranging from small business owners and managers to higher executives and proprietors of large businesses), and was mostly female, White, and right-handed.

Table 1  
*Sociodemographic Characteristics of the Current Sample (N =122)*

Variable	Statistic
Age (M, [SD])	19.68 (1.46)
Education (M, [SD])	13.02 (1.11)
Sex (female, [%])	107 (87.70)
Handedness ( <i>f</i> right, [%])	115 (94.30)
Race ( <i>f</i> , [%])	
White	58 (47.50)
Coloured	36 (29.50)
Black	9 (7.40)
Indian	17 (13.90)
Middle Eastern	1 (0.08)
Asian	1 (0.08)
Socioeconomic status ( <i>f</i> , [%])	
0	1 (0.08)
1	1 (0.08)
2	1 (0.08)
3	0 (0.00)
4	6 (4.90)
5	5 (4.10)
6	6 (4.90)
7	36 (29.50)
8	23 (18.90)
9	25 (20.50)

*Note.* Socioeconomic status (SES) was measured using Hollingshead Index, where 0 = unemployed; 1 = farm laborers and menial service workers; 2 = unskilled workers; 3 = machine operators and semiskilled workers; 4 = small business owners, skilled manual workers, craftsmen, and tenant farmers; 5 = clerical and sales workers, small farm and business owners; 6 = technicians, semiprofessionals, and small business owners; 7 = small business owners, farm owners, managers, and minor professionals; 8 = administrators, lesser professionals, and proprietors of medium-sized businesses; 9 = higher executives, proprietors of large businesses, and major professionals. SES data were available for 104 participants.

**CAT-Rapid performance.** Table 2 displays data on participants' answers to the CAT-Rapid symptom questions, and their performance on each of the different CAT-Rapid subtests, across the two modes of administration. Overall, participants performed significantly better on the paper-and-pencil CAT-Rapid. Specifically, a series of paired-sample *t*-tests detected significant between-administration differences, in favor of the paper-and-pencil version over the smartphone version, on these outcome variables: (a) trail making test score (a difference associated with a moderate effect size), (b) trail making test

time to completion (small effect size), (c) word recall score (small effect size), and (d) total score (small effect size).

A different pattern emerged with regard to symptom questions, however: Participants specified the *absence* of more symptoms on the smartphone administration than on the paper-and-pencil administration. Although this finding for between-administration differences on the *overall* symptom score was not statistically significant, a series of chi-square analyses detected significant between-administration differences with regard to participants' responses to each of the *individual* symptom questions (all of these differences were associated with large effect sizes). A series of similar analyses detected no significant-between-administration differences with regard to participants' responses to each of the individual word recall questions.

Table 2  
Overall Performance Across Both Modes of CAT-Rapid Administration ( $N = 122$ )

Variable	CAT-Rapid		$t / X^2$	$p$	ESE
	Paper-and-Pencil	Smartphone			
Symptom Questions ( $f_{yes}$ , [%])					
Do you often have problems remembering information?	40 (32.80)	37 (30.30)	69.49	< .001***	.76
Are your hands clumsy, shaky or weak?	20 (16.40)	17 (13.90)	74.38	< .001***	.78
Have you found it hard to follow a conversation or a story?	14 (11.50)	12 (9.80)	67.65	< .001***	.75
Do you have trouble doing or planning daily activities?	12 (9.80)	9 (7.40)	68.47	< .001***	.75
Symptom Questions Score ( $M$ , [ $SD$ ])	3.30 (1.00)	3.37 (0.97)	1.05	.295	-0.07
Trail Making Test					
Score ( $M$ , [ $SD$ ])	3.80 (0.61)	3.42 (0.78)	-4.29	< .001***	0.54
Time to Completion <sup>a</sup> ( $M$ , [ $SD$ ])	7.20 (3.35)	7.91 (2.79) <sup>b</sup>	2.35	.020*	-0.23
Word Recall Test ( $f_{yes}$ , [%])					
Apple	117 (95.90)	121 (99.20)	0.04	.836	.02
Watch	118 (96.70)	102 (83.60)	1.28	.529	.10
Table	105 (86.10)	104 (85.20)	7.61	.158	.18
Red	121 (99.20)	119 (97.50)	0.03	.873	.01
Word Recall Score	3.86 (0.30)	3.76 (0.40)	-2.45	.015*	0.28
Total Score ( $M$ , [ $SD$ ])	10.97 (1.26)	10.56 (1.40)	-3.52	.001**	0.31

Note. CAT-Rapid = Cognitive Assessment Tool-Rapid; ESE = estimate of effect size; in this case, Cohen's  $d$  for continuous variables and Cramer's  $V$  for categorical variables.

<sup>a</sup>Measured in seconds. Data analyzed for 121 participants due to technical malfunction of CAT-Rapid smartphone application during administration to 1 participant.

\* $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ .



**Distribution of scores within the CAT-Rapid subtests.** Table 3 displays data on the frequency of scores achieved within each subtest of the CAT-Rapid. Overall, on the smartphone administration, most participants achieved a score of 4 on the symptom questions, trail making test, and word recall test (62.30%, 57.40%, and 68.90% respectively). On the paper-and-pencil administration, the same pattern was observed: most participants achieved a score of 4 on the symptom questions, trail making test, and word recall test (59.58%, 88.50%, and 79.50% respectively).

Table 3  
*Distribution of Scores within the CAT-Rapid Subtests (N = 122)*

Subtest Score	Symptom Score		Trail Making Score		Word Recall Score <sup>a</sup>	
	Paper-and-Pencil	Smartphone	Paper-and-Pencil	Smartphone	Paper-and-Pencil	Smartphone
4	73	76	108	70	97	84
3	22	25	7	36	9	17
2	21	13	4	13	0	0
1	3	6	3	3	0	0
0	3	2	0	0	0	0

*Note.* CAT-Rapid = Cognitive Assessment Tool-Rapid. <sup>a</sup>For the smartphone administration, 19 participants had a score of 3.5 and 2 participants had a score of 2.5. For the paper-and-pencil administration, 16 participants had a score of 3.5.

**Relationship between the two versions of the CAT-Rapid.** Table 4 displays the results of a series of correlational analyses conducted to investigate whether outcome variables derived from the two different versions of the CAT-Rapid were positively associated.

As can be seen, there was a statistically significant and positive between-version association for scores on each of the four symptom questions. Similarly, there was a significant and strong positive relationship between (a) total symptom score on the paper-and-pencil version and that on the smartphone version, and (b) total overall score on the paper-and-pencil version and that on the smartphone version.

Of note here is that the significant association between the total overall scores was driven solely by the strong association between the total symptom scores: When correlating a total score that is derived solely from the addition of the trail making test and word recall scores (i.e., excluding the symptom scores and making the total possible CAT-Rapid score = 8),  $r = .04, p > .05$ . Similarly, a partial correlational analysis of the total overall scores on the two versions of the instrument, controlling for total symptom scores, produced a result of  $r = -.01, p > .05$ .

As Table 3 shows, there was no significant association for trail making test scores and word recall scores (individual items as well as total score). There was, however, a significant and positive between-version association for time to complete the trail making test.

Table 4  
*Relationship between the Two Versions of the CAT-Rapid (N =122)*

CAT-Rapid Item	<i>r</i>
Symptom questions <sup>a</sup>	
Do you have trouble remembering information?	.755**
Are your hands clumsy, shaky, or weak?	.781**
Do you find it hard to follow a conversation or a story?	.745**
Do you have trouble doing or planning daily activities?	.749**
Total symptom score <sup>b</sup>	.757**
Trail making test	
Score <sup>b</sup>	.001
Time <sup>b,c</sup>	.325**
Word recall test <sup>a</sup>	
Apple	-.019
Watch	.051
Table	-.023
Red	-.014
Total score <sup>b</sup>	
CAT-Rapid Total Score <sup>b</sup>	.544**

*Note.* CAT-Rapid = Cognitive Assessment Tool-Rapid. Maximum score on this instrument = 12. Maximum score on the symptom questions, trail making test, and word recall test = 4 points each.

<sup>a</sup>Spearman's *rho* correlation coefficient used for non-continuous variables.

<sup>b</sup>Pearson's product-moment correlation coefficient used for continuous variables.

<sup>c</sup>Data analysed for 121 participants due to technical malfunction of CAT-Rapid smartphone application during administration to 1 participant.

\* $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ . All  $p$ -values are two-tailed.

**Construct validity of the two versions of the CAT-Rapid.** Table 5 displays the results of a series of correlational analyses relevant to Hypotheses 1, 2, 3, and 4, addressing the construct validity of the CAT-Rapid trail making and word recall subtests in a cognitively healthy young adult sample.

Regarding Hypothesis 1 (that the correlation between performance on the trail making test of the paper-and-pencil CAT-Rapid and performance on an analogous standardized paper-and-pencil neuropsychological test [CTT Part 2] will be significantly different from zero), the prediction was confirmed: There was a significant, albeit weak, positive relationship between the two outcome variables of interest.

Regarding Hypothesis 2 (that the correlation between performance on the trail making test of the smartphone CAT-Rapid and performance on an analogous standardized paper-and-pencil neuropsychological test [CTT Part 2] will be significantly different from zero), the prediction was confirmed: There was a significant, albeit weak, positive relationship between the two outcome variables of interest.

Regarding Hypothesis 3 (that the correlation between the word recall score on the paper-and-pencil CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test [HVLTR delayed recall trial] will be significantly different from zero), the prediction was confirmed: There was a significant, albeit weak, positive relationship between the two outcome variables of interest.

Regarding Hypothesis 4 (that the correlation between the word recall score on the smartphone CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test [HVLTR delayed recall trial] will be significantly different from zero), the prediction was confirmed: there was a significant, albeit weak, positive relationship between the two outcome variables of interest.

Table 5  
*Construct Validity of CAT-Rapid Trail Making Test and Word Recall Subtests (N = 122)*

CAT-Rapid Variable	Color Trails Test Part 2	HVLTR Delayed Recall
Paper-and-pencil		
Trail making test	.179*	----
Word recall total	----	.322**
Smartphone		
Trail making test <sup>a</sup>	.286**	----
Word recall total	----	.245**

*Note.* Data presented are Pearson's  $r$  correlation coefficients for associations between raw scores on (a) time to completion on the CAT-Rapid trail making test and that on the Color Trails Test Part 2, and (b) total score on the CAT-Rapid word recall test and that on the HVLTR delayed recall trial. CAT-Rapid = Cognitive Assessment Tool-Rapid. HVLTR = Hopkins Verbal Learning Test-Revised.

<sup>a</sup>Data analysed for 121 participants due to technical malfunction of CAT-Rapid smartphone application during administration to 1 participant.

\* $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ . All  $p$ -values are two-tailed.

**Post-hoc exploratory analyses.** Additional analyses explored the relationship between performance on the WAIS-III Digit Span Forward Subtest (a measure of attention), WAIS-III Digit Span Backward Subtest (a measure of working memory), and the WAIS-III Digit Symbol Coding Subtest (a measure of information processing speed), as these are all neuropsychological domains affected by HIV. These analyses were conducted to test the assumption that objective performance in the cognitive domains of attention, working memory, and processing speed would be potential contributors to overall performance on the CAT-Rapid.

Table 6 displays the results of a series of correlational analyses examining the relationship between CAT-Rapid total score and raw scores on, respectively, tests of auditory attention (WAIS-III Digit Span Forward), working memory (WAIS-III Digit Span Backward), and information processing speed (WAIS-III Digit Symbol Coding).

Regarding the paper-and-pencil CAT-Rapid administration, there were significant and positive (but relatively weak) relationships between total score on the instrument and raw scores on the tests of attention and of information processing speed. There was no significant relationship between paper-and-pencil CAT-Rapid total score and raw score on the test of working memory.

Regarding the smartphone CAT-Rapid administration, there were significant and positive (but, again, relatively weak) relationships between total score on the instrument and raw scores on each of the WAIS-III subtests.

Table 6  
*Relationship between CAT-Rapid Total Score and Performance on Tests of Attention, Working Memory, and Information Processing (N = 122)*

WAIS-III Subtest	CAT-Rapid Total Score	
	Paper-and-Pencil	Smartphone
Digit Span		
Forward	.287**	.254**
Backward	.117	.244**
Digit Symbol Coding	.185*	.288**

*Note.* CAT-Rapid = Cognitive Assessment Tool-Rapid. Data presented are Pearson's  $r$  correlation coefficients.

\* $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ . All listed  $p$ -values are two-tailed.

## **Study 2: Construct and Diagnostic Validity of the Paper-and-Pencil CAT-Rapid in an HIV-Positive Sample**

**Sample characteristics.** Table 7 displays sociodemographic and clinical characteristics of this study's sample. The sample consisted entirely of HIV-positive Black South Africans, with isiXhosa as a home language, from low-SES backgrounds. Overall, the sample (a) was aged between 23 and 49 years ( $M = 33.47$ ,  $SD = 5.90$ ), (b) had between 6 and 14 years of education ( $M = 10.29$ ,  $SD = 1.47$ ), (c) was mostly female ( $n = 80$  females; 89.9%), (d) was mostly right-handed ( $n = 84$  right-handed; 94.4%), and (e) had a CD4 cell count of between 24 and 857 cells/ml ( $M = 354.14$ ,  $SD = 206.35$ ).

I conducted a series of one-way ANOVAs that sought to detect whether there were significant between-group differences for each of the continuous sociodemographic and clinical variables (viz., age, highest level of education, CD4 cell count). Regarding assumptions pertaining to those analyses, equal variances and independence of observations were both upheld; the assumption of normally distributed data was not, however. More specifically, the data distribution within each group for all three continuous variables was not normal. However, I proceeded with the conventional analysis due to the robust nature of ANOVA. For between-group comparisons of the categorical variables (viz., sex, handedness), I used Fisher's exact tests as the assumption of expected cell frequencies greater than 5 was not upheld.

Overall, there were no significant between-group differences for any of the categorical variables (viz., sex, handedness), and for two out of the three continuous variables (viz., age, CD4 cell count). All of those differences were associated with small effect sizes. However, the analysis detected a significant between-group difference with regard to highest level of education (although that difference was also associated with a small effect size). Hence, I used the Games-Howell post-hoc procedure to determine where the largest between-group differences with regard to level of education lay. The results of that analysis suggested that participants in the CU group had, on average, significantly more years of education than those in the MND group,  $p < .05$ .

Table 7  
*Sociodemographic and Clinical Characteristics of the Current Sample (N = 89)*

Variable	CU (n = 39)	ANI (n = 24)	MND (n = 22)	HIV-D (n = 4)	F / X <sup>2</sup>	p	ESE
Age (years) <sup>a</sup>							
M (SD)	33.16 (5.52)	32.57 (6.21)	33.91 (6.20)	39.25 (4.11)	1.57	.20	.05
Interquartile range	6.50	8.00	10.00	7.75			
Education <sup>a,b</sup>							
M (SD)	10.90 (1.12)	9.91 (1.51)	9.82 (1.50)	9.00 (2.16)	5.12	< .01**	.16
Interquartile range	2.00	2.00	2.25	4.00			
Sex							
Female (f, [%])	36 (92.30)	22 (91.70)	19 (86.40)	3 (75.00)	2.27	.49	.14
Male (f, [%])	3 (7.70)	2 (8.30)	3 (13.60)	1 (25.00)			
Handedness							
Right (f, [%])	37 (94.90)	22 (91.70)	21 (95.50)	4 (100.00)	0.91	.88	.09
Left (f, [%])	2 (5.10)	2 (8.30)	1 (4.50)	0 (0.00)			
CD4 count (cells/ml) <sup>c</sup>							
M (SD)	336.38 (224.17)	397.13 (147.27)	315.50 (201.26)	---- <sup>d</sup>	0.67	.57	.04
Interquartile range	351.50	281.00	285.75	---- <sup>d</sup>			

*Note.* CU = cognitively unimpaired; ANI = asymptomatic neurocognitive impairment; MND = mild neurocognitive disorder; HIV-D = HIV-dementia; ESE = estimate of effect size; in this case, eta squared for continuous variables and Cramer's *V* for categorical variables.

<sup>a</sup>Data available for 87 participants. For the variable *Age*, data were missing for one participant in the CI group and one participant in the ANI group. For the variable *Education*, data were missing for two participants in the ANI group.

<sup>b</sup>Number of years of successfully completed education.

<sup>c</sup>Data available for 57 participants: 32 in the CU group, 16 ANI, 8 MND, and 1 HIV-D. CD4 count for the latter participant was 544 cells/ml.

<sup>d</sup>Analyses not attempted as data only available for 1 participant in HIV-D group.

\* $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ .



**CAT-Rapid performance.** Table 8 displays data on participants' answers to the CAT-Rapid symptom questions, and their performance on each of the different CAT-Rapid subtests. Overall, participants in the ANI group performed better in terms of (a) total score, (b) total number of symptom questions to which they responded negatively, and (c) word recall score; then followed the CU, MND, and HIV-D groups, respectively. Regarding the trail making test, participants in the HIV-D group performed best, followed by the MND, ANI, and CU groups, respectively. Regarding performance on the HVLT-R delayed recall trial, participants in the CU group scored the highest, followed by the ANI, MND, and HIV-D groups, respectively.

I also conducted a series of one-way ANOVAs that sought to detect whether there were significant between-group differences for each of the continuous CAT-Rapid and neuropsychological test outcome variables. Regarding assumptions pertaining to those analyses, equal variances and independence of observations were both upheld; the assumption of normally distributed data was not, however. More specifically, the data distribution within each group for all five continuous variables was not normal. However, I proceeded with the analyses in the conventional manner due to the robust nature of ANOVA. For between-group comparisons of the categorical variables (viz., each of the symptom and word recall questions of the CAT-Rapid), I used Fisher's exact tests as the assumption of expected cell frequencies greater than 5 was not upheld.

Table 8 shows that the analyses detected no significant between-group differences for trail making test score and word recall score. Both comparisons were associated with small effect sizes. However, the analysis detected significant between-group differences with regard to the total symptom questions score, the total CAT-Rapid score, and the HVLT-R delayed recall score (all of these differences were associated with a small effect size).

For each of these latter three outcome variables, I used the Games-Howell post-hoc procedure to determine where the largest between-group differences lay. Regarding the total symptom questions score, the analysis detected suggested that, on average, participants in the MND group endorsed the presence of significantly more symptoms than did those in the ANI group,  $p < .05$ . Regarding the CAT-Rapid total score, the analysis detected no significantly different pairs of means, and, further, no trends toward significance for any of the comparisons. Regarding the HVLT-R delayed recall trial score, the analysis detected significant differences ( $p < .05$ ) between (a) the CU and ANI groups, and (b) the CU and MND groups. Specifically, participants in the ANI and MND groups recalled fewer words on that trial than did those in the CU group.

A series of chi-square analyses detected significant between-group differences with regard to participants' responses to three of the four individual symptom questions (all of these differences were associated with small effect sizes). The analysis detected no significant between-group differences with regard to participants' responses to the words *watch* and *table* (both of these differences were associated with small effect sizes). Data for the words *apple* and *red* were not analyzed because participants for whom such data were available all recalled these words correctly.

Table 8  
*Overall Performance and Between-Group Differences on the Various CAT-Rapid Tests (N = 89)*

CAT-Rapid / Neuropsychological Test Variable	CU (n = 39)	ANI (n = 24)	MND (n = 22)	HIV-D (n = 4)	F / $\chi^2$	p	ESE
Symptom Questions ( <i>f</i> yes, [%])							
Do you often have problems remembering information?	16 (41.00)	4 (16.70)	12 (54.50)	4 (100.00)	13.12	.003**	.39
Are your hands clumsy, shaky or weak?	4 (10.30)	5 (20.80)	7 (31.80)	3 (75.00)	9.94	.014*	.35
Have you found it hard to follow a conversation or a story?	11 (28.20)	5 (20.80)	10 (45.50)	2 (50.00)	4.17	.23	.21
Do you have trouble doing or planning daily activities?	6 (15.40)	3 (12.50)	11 (50.00)	2 (50.00)	11.85	.006**	.38
Symptom Questions Score ( <i>M</i> , [ <i>SD</i> ])	3.05 (1.00)	3.29 (1.08)	2.23 (1.48)	1.25 (1.50)	6.03	.001**	.18
Trail Making Test Score ( <i>M</i> , [ <i>SD</i> ])	3.26 (1.07)	3.29 (0.90)	3.45 (1.06)	3.50 (1.00)	0.23	.88	.01
Word Recall ( <i>f</i> yes, [%]) <sup>a</sup>							
Apple	23 (59.00)	17 (70.80)	9 (40.90)	2 (50.00)	--- <sup>b</sup>	--- <sup>b</sup>	--- <sup>b</sup>
Watch	22 (56.40)	16 (66.70)	9 (40.90)	1 (25.00)	9.57	.11	.37
Table	22 (56.40)	17 (70.80)	9 (40.90)	2 (50.00)	3.00	1.00	.16
Red	23 (59.00)	17 (70.80)	9 (40.90)	2 (50.00)	--- <sup>b</sup>	--- <sup>b</sup>	--- <sup>b</sup>
Word Recall Score ( <i>M</i> , [ <i>SD</i> ])	3.64 (0.47)	3.77 (0.39)	3.48 (0.55)	3.38 (0.48)	1.88	.14	.06
Total Score ( <i>M</i> , [ <i>SD</i> ])	10.01 (1.71)	10.23 (1.93)	9.05 (1.98)	8.13 (1.93)	2.90	.04*	.09
HVLT-R Delayed Recall Score ( <i>M</i> , [ <i>SD</i> ])	8.95 (1.47)	7.58 (1.67)	7.05 (1.50)	6.75 (2.06)	9.04	< .001***	.24

*Note.* CAT-Rapid = Cognitive Assessment Tool-Rapid. CU = cognitively unimpaired; ANI = asymptomatic neurocognitive impairment; MND = mild neurocognitive disorder; HIV-D = HIV-dementia; ESE = estimate of effect size; in this case,  $\eta^2$  for continuous variables and Cramer's *V* for categorical variables.

<sup>a</sup>Data only available for 51 participants due to administration error by the examiner: 23 in the CU group, 17 ANI, 9 MND, and 2 HIV-D.

<sup>b</sup>Analyses not attempted due to the fact that all participants for whom data were available correctly recalled these words.

\* $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ .

### **Predicting overall CAT-Rapid performance from CAT-Rapid symptom**

**questions.** Table 9 displays the results of a four-step hierarchical multiple regression analysis addressing the question of how strongly responses to the CAT-Rapid symptom questions were predictive of the CAT-Rapid subtotal score (i.e., the total score minus the total symptom score, as if the instrument consisted only of the trail making and word recall subtests, and thus had a maximum total possible score of 8).

The model determined, at Step 1, that the symptom question “*Do you often have problems remembering information?*” was not a significant predictor of the CAT-Rapid subtotal score, accounting for 0.4% of the variance in the outcome. Introducing the symptom question “*Are your hands clumsy, shaky, or weak?*” to the model accounted for an additional 0.1% of variance in the outcome. Introducing the symptom question “*Have you found it hard to follow a conversation or a story?*” to the model accounted for no additional variance in the outcome. Lastly, introducing the symptom question, “*Do you have trouble doing or planning daily activities?*” to the model accounted for an additional 3.3% of the variance in the outcome. Taken together, the four symptom questions accounted for 3.8% of the variance in the paper-and-pencil CAT-Rapid subtotal score,  $F(1, 84) = 2.84, p = .10$ .

Table 9  
*Predicting CAT-Rapid Subtotal Score (out of 8) from CAT-Rapid Symptom Questions (N = 89)*

Variable	B	SE B	$\beta$
Step 1			
Constant	6.86	.19	
Do you often have problems remembering information?	0.15	.24	.07
Step 2			
Constant	6.82	.28	
Do you often have problems remembering information?	0.14	.25	.06
Are your hands clumsy, shaky, or weak?	0.06	.30	.02
Step 3			
Constant	6.83	.30	
Do you often have problems remembering information?	0.14	.26	.06
Are your hands clumsy, shaky, or weak?	0.07	.31	.03
Have you found it hard to follow a conversation or a story?	-0.03	.28	-.01
Step 4			
Constant	6.68	.31	
Do you often have problems remembering information?	0.02	0.27	.01
Are your hands clumsy, shaky, or weak?	-0.09	.33	-.03
Have you found it hard to follow a conversation or a story?	-0.13	.28	-.05
Do you have trouble doing or planning daily activities?	0.55	.33	.21

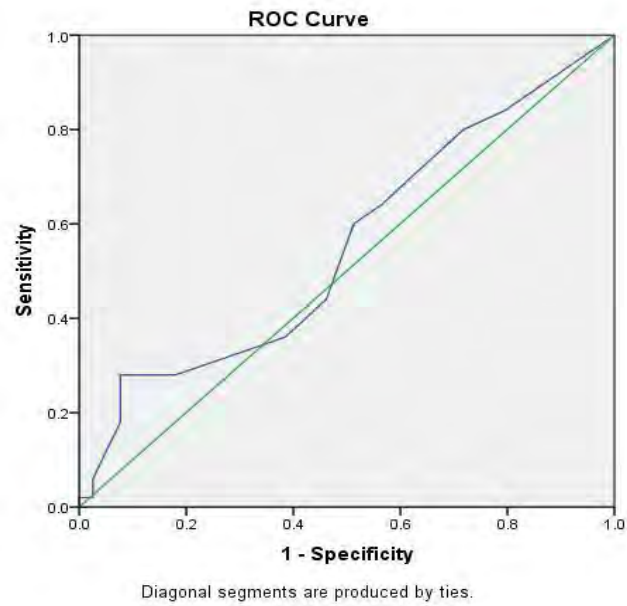
*Note.* CAT-Rapid = Cognitive Assessment Tool-Rapid.  $R^2 = < .01$  for Step 1,  $\Delta R^2 = < .01$  for Step 2 ( $p = .83$ ),  $\Delta R^2 = < .001$  for Step 3 ( $p = .91$ ),  $\Delta R^2 = .03$  for Step 4 ( $p = .10$ ).

\* $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ .

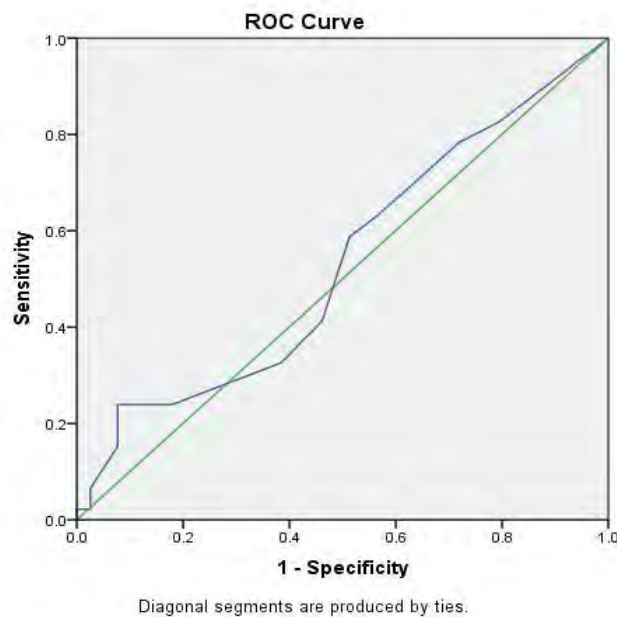
**Construct validity of the CAT-Rapid.** Recall that, in this sample, time to complete the CAT-Rapid trail making test was not recorded, and so construct validity information is only available for the word recall subtest. Hence, Hypothesis 5 stated that, across the entire sample, the correlation between the word recall score on the paper-and-pencil CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test (HVLT-R delayed recall trial) will be significantly different from zero. This prediction was not confirmed: There was a non-significant and weak positive relationship between the two outcome variables of interest,  $r = .16$ ,  $p = .13$

**Diagnostic validity of the CAT-Rapid.** Analysis of the diagnostic validity of the CAT-Rapid proceeded across three stages: (1) preliminary analyses utilizing ROC curves; (2) main analyses addressing the hypotheses in question; and (3) post-hoc analyses exploring alternative cut-off points for the instrument.

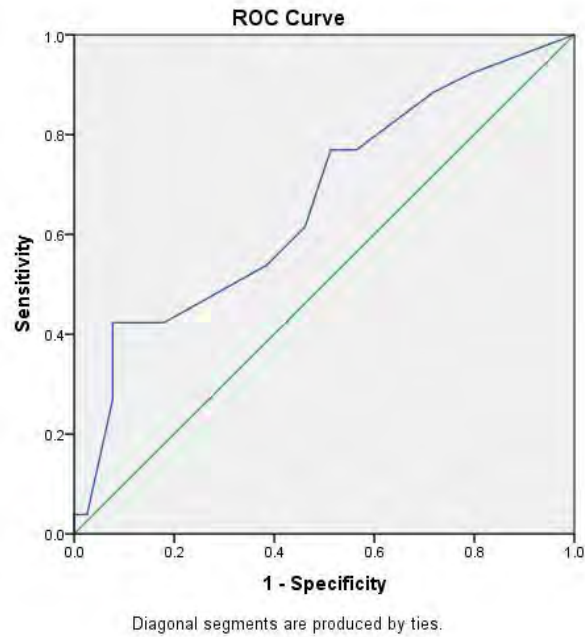
*Analysis stage 1: Preliminary ROC curve analyses.* To achieve an overall sense of the diagnostic capabilities of the tool, I produced ROC curves for the following differential diagnoses: (1) CU versus HAND (see Figure 1); (2) CU versus mild HAND (see Figure 2); (3) CU versus symptomatic HAND (see Figure 3); and (4) CU versus HIV-D (see Figure 4).



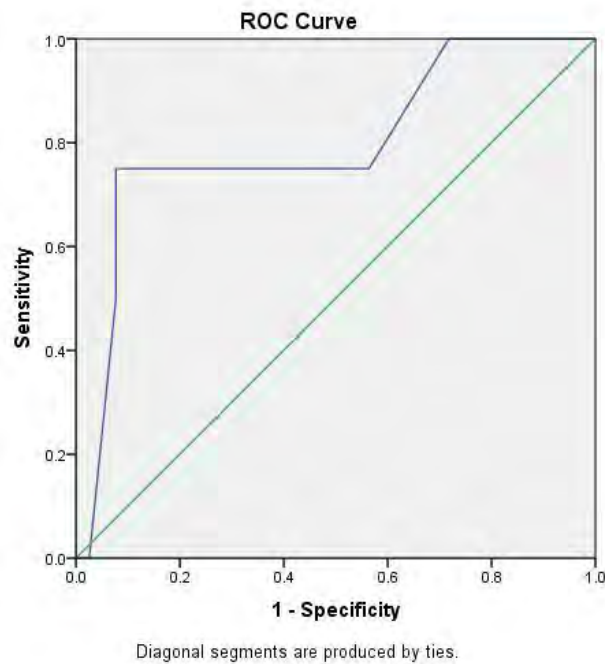
*Figure 1.* Receiver operating characteristic (ROC) curve of CAT-Rapid cut-off scores for distinguishing HAND patients (viz., all participants in the ANI, MND, and HIV-D groups, taken together) from participants in the CU group. The diagonal reference line represents the AUC, which had a value of .553.



*Figure 2.* Receiver operating characteristic (ROC) curve of CAT-Rapid cut-off scores for distinguishing the group of mild HAND patients (viz., those with ANI and MND) from participants in the CU group. The diagonal reference line represents the AUC, which had a value of .532.



*Figure 3.* Receiver operating characteristic (ROC) curve of CAT-Rapid cut-off scores for distinguishing the group of symptomatic HAND patients (viz., those with MND and HIV-D) from participants in the CU group. The diagonal reference line represents the AUC, which had a value of .664.



*Figure 4.* Receiver operating characteristic (ROC) curve of CAT-Rapid cut-off scores for distinguishing participants in the HIV-D group from those in the CU group. The diagonal reference line represents the AUC, which had a value of .795.



The AUC was only statistically significant for the differential diagnosis of CU versus symptomatic HAND ( $p = .03$ ), indicating that the instrument only had a significant discriminatory capacity in terms of sensitivity and specificity for this differential. The AUC values associated with the ROC curves for the other three differential diagnoses were not statistically significant, indicating that the instrument did not have significant discriminatory capacity in terms of sensitivity and specificity for those differentials.

Table 10 displays a summary of the results of the series of ROC analyses with accompanying cut-off scores. In clinical settings, a higher sensitivity value is most important; therefore, I selected optimal cut-off scores by choosing the highest sensitivity possible (and therefore maximizing the tool's accuracy in detecting HAND participants), and, in turn, compromising specificity (and therefore placing less emphasis on the tool's accuracy in confirming that CU participants were, in fact, unimpaired). These cut-off scores are indicated in boldface font in the Table.

Table 10

Summary of the Receiver Operating Characteristic (ROC) Curve Analyses, with Cut-off Scores for the CAT-Rapid (N = 89)

Differential Diagnosis	AUC (SE)	p	95% CI	Cut-off score	Sensitivity	1 - Specificity
CU vs. HAND	.55 (.06)	.39	.43 - .67	9.25	.36	.39
				9.75	.44	.46
				10.25	.60	.51
				10.75	.64	.56
				<b>11.25</b>	<b>.80</b>	<b>.72</b>
				11.75	.84	.80
CU vs. Mild <sup>a</sup>	.53 (.06)	.62	.41 - .66	9.25	.33	.36
				9.75	.41	.46
				10.25	.59	.51
				10.75	.63	.56
				<b>11.25</b>	<b>.78</b>	<b>.72</b>
				11.75	.83	.80
CU vs. Symptomatic <sup>b</sup>	.66 (.07)	.03*	.53 - .80	9.25	.54	.39
				9.75	.62	.46
				10.25	.77	.51
				10.75	.77	.56
				<b>11.25</b>	<b>.89</b>	<b>.72</b>
				11.75	.92	.80
CU vs. HIV-D	.80 (.13)	.05	.54 - 1.00	9.25	.75	.39
				9.75	.75	.46
				10.25	.75	.51
				10.75	.75	.56
				<b>11.25</b>	<b>1.00</b>	<b>.72</b>
				11.75	1.00	.80

Note. CAT-Rapid = Cognitive Assessment Tool-Rapid. CU = cognitively unimpaired; HAND = HIV-associated neurocognitive disorder; HIV-D = HIV-dementia.

<sup>a</sup>Milder forms of HAND (viz., patients with ANI or MND).

<sup>b</sup>Symptomatic forms of HAND (viz., patients with MND or HIV-D).

\* $p < .05$ . \*\* $p < .01$ . \*\*\* $p < .001$ .

**Analysis stage 2: Diagnostic validity of the CAT-Rapid at the recommended cut-off score of  $\leq 10$ .** Hypothesis 6 stated that, at the recommended cut-off score of  $\leq 10$  (Joska, 2013), the paper-and-pencil CAT-Rapid will display high sensitivity and specificity in differentially diagnosing individuals in the following HAND categories from CU individuals: (a) all three forms of HAND (ANI, MND, HIV-D); (b) the milder forms of HAND (ANI, MND); (c) symptomatic HAND (MND, HIV-D); and (d) HIV-D. To test that hypothesis, I conducted diagnostic analyses using SPSS-generated 2 x 2 contingency tables and an online diagnostic calculator.

Table 11 presents the resulting sensitivity, specificity, PPV, and NPV data. Overall, the a priori prediction was not confirmed: The CAT-Rapid displayed suboptimal diagnostic properties for all tested differential diagnoses. Specifically, at the recommended cut-off score of  $\leq 10$ , the CAT-Rapid discriminated best between the CU and symptomatic HAND participants (i.e., had the highest combination of sensitivity and specificity). Next best was the instrument's ability to discriminate between the CU participants and those diagnosed with HIV-D. The CAT-Rapid showed poor ability to discriminate between the CU participants and those diagnosed with any form of HAND, and presented with the lowest combination of sensitivity and specificity when attempting to discriminate between the CU participants and those diagnosed with mild HAND.

Table 11

*Diagnostic Validity of the Paper-and-Pencil CAT-Rapid at a Cut-Off Point of  $\leq 10$  (N = 89)*

Differential Diagnosis	Sensitivity	Specificity	PPV	NPV
CU vs. HAND	60.00%	48.72%	60.00%	48.72%
CU vs. Mild <sup>a</sup>	58.70%	48.72%	57.45%	50.00%
CU vs. Symptomatic <sup>b</sup>	76.92%	48.72%	50.00%	76.00%
CU vs. HIV-D	75.00%	48.72%	13.04%	95.00%

*Note.* CAT-Rapid = Cognitive Assessment Tool-Rapid; CU = cognitively unimpaired; PPV = positive predictive value; NPV = negative predictive value; HAND = HIV-associated neurocognitive disorder; HIV-D = HIV-dementia.

<sup>a</sup>Milder forms of HAND (viz., patients with ANI or MND).

<sup>b</sup>Symptomatic forms of HAND (viz., patients with MND or HIV-D).

**Analysis stage 3: Post-hoc exploratory analyses.** Table 12 displays the results of a series of additional diagnostic analyses conducted to determine whether adjusting the CAT-Rapid's cut-off score would improve its diagnostic properties. As can be seen, at a

cut-off score of  $\leq 9.5$ , the CAT-Rapid did not discriminate better, in comparison to the recommended cut-off score of  $\leq 10$ , between CU participants and those with (a) any form of HAND; (b) milder forms of HAND; and (c) symptomatic forms of HAND. More specifically, while specificity values for this cut-off score increased relative to those for the recommended cut-off score, sensitivity values decreased.

At a cut-off score of  $\leq 10.5$ , the CAT-Rapid showed, in terms of sensitivity, better ability to discriminate, in comparison to the recommended cut-off score of  $\leq 10$ , between CU participants and those with (a) any of the three forms of HAND, and (b) those with the milder forms of HAND. However, specificity values for those two differential diagnoses decreased relative to those for the recommended cut-off score. Furthermore, a cut-off score of  $\leq 10.5$  did not improve or worsen, in terms of sensitivity, the tool's ability to distinguish CU participants from (a) those with symptomatic HAND, or (b) those with HIV-D.

At a cut-off score of  $\leq 11$ , the CAT-Rapid showed, in terms of sensitivity, better ability to discriminate, in comparison to the recommended cut-off score of  $\leq 10$ , between CU participants and all of the different HAND groups. More specifically, a cut-off score of  $\leq 11$  had the highest sensitivity for CU versus HIV-dementia, followed by CU versus symptomatic HAND, then CU versus any form of HAND, and finally CU versus mild HAND. However, in comparison to the recommended cut-off score of  $\leq 10$ , the specificity values for this cut-off score are extremely poor.

Table 12  
*Diagnostic Validity of the Paper-and-Pencil CAT-Rapid at Various Cut-Off Points (N = 89)*

Cut-off Value / Differential Diagnosis	Sensitivity	Specificity	PPV	NPV
CAT-Rapid $\leq$ 9.5				
CU vs. HAND	44.00%	53.85%	55.00%	42.86%
CU vs. Mild <sup>a</sup>	41.30%	53.85%	51.35%	43.75%
CU vs. Symptomatic <sup>b</sup>	61.54%	53.85%	47.06%	67.74%
CU vs. HIV-D	75.00%	53.85%	14.29%	95.45%
CAT-Rapid $\leq$ 10.5				
CU vs. HAND	64.00%	43.59%	59.26%	48.57%
CU vs. Mild <sup>a</sup>	63.04%	43.59%	56.86%	50.00%
CU vs. Symptomatic <sup>b</sup>	76.92%	43.59%	47.62%	73.91%
CU vs. HIV-D	75.00%	43.59%	12.00%	94.44%
CAT-Rapid $\leq$ 11				
CU vs. HAND	80.00%	28.21%	58.82%	52.38%
CU vs. Mild <sup>a</sup>	78.26%	28.21%	56.52%	52.38%
CU vs. Symptomatic <sup>b</sup>	88.46%	28.21%	45.10%	78.57%
CU vs. HIV-D	100.00%	28.21%	12.50%	100.00%

*Note.* CAT-Rapid = Cognitive Assessment Tool-Rapid;; PPV = positive predictive value; NPV = negative predictive value; CU = cognitively unimpaired; HAND = HIV-associated neurocognitive disorder; HIV-D = HIV-dementia.

<sup>a</sup>Milder forms of HAND (viz., patients with ANI or MND).

<sup>b</sup>Symptomatic forms of HAND (viz., patients with MND or HIV-D).

## Discussion

The purpose of this study was to validate the CAT-Rapid (Joska, 2013), a screening tool designed to assess cognitive impairment due to HIV. Two separate studies tested the CAT-Rapid's construct and diagnostic validity.

### Study 1: Examining Construct Validity of the CAT-Rapid in a Cognitively Healthy Sample of University Undergraduate Students

The main purpose of Study 1 was to investigate construct validity of the CAT-Rapid by examining whether CAT-Rapid subtest scores (from both paper-and-pencil and smartphone administrations) correlated with scores on standardized paper-and-pencil

tests that assess the domains of cognitive functioning purportedly measured by the screening tool. I tested four hypotheses, all of which were related to the correlations of CAT-Rapid subtest scores with scores on standardized paper-and-pencil neuropsychological tests.

**CAT-Rapid performance within and between the two different versions.**

Before testing the a priori hypotheses and hence investigating construct validity properties of the screening tool, I performed some preliminary analyses in order to (a) achieve an overall understanding of performance on both administrations of the instrument, and (b) determine whether outcome variables derived from the two different administrations were associated positively.

Although initial analyses indicated a significant and strong positive correlation between total scores on the paper-and-pencil and smartphone administrations of the CAT-Rapid, follow-up analyses determined that this correlation was driven almost entirely by the strong between-administration association of total symptom scores. (Recall that the CAT-Rapid total possible score of 12 includes a total symptom score ranging from 0-4.) After total symptom scores were removed from the analysis, there was no longer a significant association between total paper-and-pencil score and total smartphone score.

When considering each individual CAT-Rapid cognitive outcome variable, participants performed significantly better on the paper-and-pencil administration than on the smartphone administration. Specifically, they attained higher trail making test scores and higher word recall scores, and completed the trail making test more rapidly, during the paper-and-pencil administration than during the smartphone administration. One explanation for the variation in performance according to mode of administration is the technical aspects associated with the smartphone administration (e.g., the relatively small screen size).

Interestingly, participants also declared the *absence* of more cognitive symptoms on the smartphone administration than on the paper-and-pencil administration: For each of the four individual symptom questions, participants' responses differed significantly across the two modes of administration, with participants endorsing the presence of a symptom more frequently during the paper-and-pencil administration than during the

smartphone administration. (The total symptom score was highly correlated across the two versions of the instrument, however.) Perhaps the most plausible explanation for this pattern of data is random variation. Such an explanation is plausible, given that the overall symptom score did not change from one administration to the next.

In conclusion, the two versions of the CAT-Rapid appear sufficiently different (i.e., there is an absence of a significant between-version correlation in performance on the trail making and word recall subtests) to not be considered as parallel versions of the same screening tool. This is an important note for potential users in clinical practice, as it suggests that in order to achieve comparable results across clinic settings and across patients, the developer of the CAT-Rapid should market only one form of administration. This way, test administrators use one version of the instrument consistently when screening patients, both within and between clinics.

**Evidence for construct validity of the CAT-Rapid.** Hypotheses 1 and 2 stated that the correlation between performance on the trail making test of, respectively, the paper-and-pencil and smartphone CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test (CTT Part 2) will be significantly different from zero. These hypotheses were confirmed: In each case, there was a statistically significant correlation between the CAT-Rapid and CTT outcome variables. This finding provides evidence for convergent validity of the CAT-Rapid trail making test, as performance was significantly similar to that on a well-established measure of visual attention and set-shifting. Overall, then, the CAT-Rapid trail making test appears to assess performance in the cognitive domains of visual attention and set-shifting.

These findings regarding the convergent validity of the CAT-Rapid trail making test are similar to those reported by Robbins et al. (2014) regarding the NeuroScreen trail making subtest and an analogous standardized paper-and-pencil neuropsychological test (Trail Making Test part B). In their sample of American HIV-positive participants, there was a statistically significant correlation between these two outcome variables.

Hypotheses 3 and 4 stated that the correlation between performance on the word recall subtest of, respectively, the paper-and-pencil CAT-Rapid and the smartphone CAT-Rapid and that on an analogous standardized paper-and-pencil neuropsychological test (HVLTR delayed recall trial) will be significantly different from zero. These

hypotheses were confirmed: In each case, there was a statistically significant correlation between the CAT-Rapid outcome variable and the HVLТ-R outcome variable. This finding provides evidence for convergent validity of the CAT-Rapid word recall subtest, as performance was significantly similar to that on a well-established measure of verbal learning and memory. Overall, then, the CAT-Rapid word recall subtest appears to assess performance in the cognitive domain of verbal learning and memory.

These findings regarding the convergent validity of the CAT-Rapid word recall subtest are similar to those reported by Joska et al. (2011) regarding the IHDS word recall subtest, and Robbins et al. (2014) regarding the NeuroScreen word recall subtest. Regarding the IHDS, in a sample of HIV-positive South African participants, there was a statistically significant correlation between performance on the IHDS word recall subtest and that on the HVLТ delayed recall trial (Joska et al., 2011). Regarding NeuroScreen, in a sample of HIV-positive American participants, there was a statistically significant correlation between performance on the NeuroScreen word recall subtest and that on the HVLТ delayed recall trial (Robbins et al., 2014).

It is noteworthy that despite the significant correlations between the CAT-Rapid subtests and analogous paper-and-pencil neuropsychological tests, these correlations were, overall, weak. Furthermore, due to the brevity of the CAT-Rapid, this screening tool has a limited range in scores; such a limitation might impact the observed correlations.

**Other contributions to performance on the CAT-Rapid.** I investigated the degree to which objective performance in the cognitive domains of attention, working memory, and processing speed, contributed to overall performance on the CAT-Rapid. Note that these additional investigations did not contribute to testing the a priori hypotheses. However, they were conducted in order to determine how well the CAT-Rapid can detect areas of cognitive impairment particularly affected by HIV. Such data are valuable for an instrument that will be utilized in clinical settings for diagnostic purposes.

Analyses suggested that (a) overall performance on the paper-and-pencil CAT-Rapid was significantly associated with performance on measures of attention and information processing speed, but not working memory, and (b) overall performance on



the smartphone CAT-Rapid was significantly associated with performance on measures of attention, working memory, and information processing speed. Overall, these findings suggest that the CAT-Rapid is sensitive to (many of) the cognitive domains typically affected in HIV, and is therefore useful for clinical (preliminary diagnostic) purposes.

### **Study 2: Examining Construct and Diagnostic Validity of the CAT-Rapid in a Clinical Sample of HIV-Positive Participants**

The purpose of Study 2 was to investigate the construct and diagnostic validity of the paper-and-pencil CAT-Rapid in a sample of 89 HIV-positive participants. These participants were classified into the following AAN-based categories (Antinori et al., 2007): (a) cognitively unimpaired (CU), (b) any of the three forms of HAND (viz., ANI, MND, HIV-D), (c) the milder forms of HAND (viz., ANI, MND), and (d) HIV-dementia (HIV-D). I tested two hypotheses, one related to the correlation between performance on the CAT-Rapid word recall subtest and that on an analogous standardized paper-and-pencil neuropsychological test, and the other related to the CAT-Rapid's ability to distinguish patients with various forms of HAND from those with no cognitive impairment.

**Overall performance on the CAT-Rapid.** I examined between-group differences in performance on the various CAT-Rapid outcome variables. Participants in the ANI group performed best on (a) total score, (b) total symptom score (i.e., they endorsed the fewest symptoms), and (c) word recall score; then followed the CU, MND, and HIV-D groups, respectively. Regarding the trail making test, participants in the HIV-D group performed best, followed by the MND, ANI, and CU groups, respectively. This unusual pattern of findings might be explained by the unequal sample sizes across the different groups. In other words, a sample size of only 4 participants in the HIV-D group detracts from the statistical power of the analysis, rendering any comparisons with this sample unreliable.

Furthermore, the fact that participants in the various HAND groups outperformed those in the CU group is problematic for diagnostic interpretations based on this instrument. Diagnostic properties are determined according to the tool's ability to distinguish between CU patients and those with HAND. However, if the CU reference

group is, on average, performing worse than the HAND groups on the CAT-Rapid, it is possible that the tool could be falsely diagnosing CU patients.

Regarding performance on the HVLT-R delayed recall trial, participants in the CU group scored the highest, followed by the ANI, MND, and HIV-D groups, respectively. A closer look at the significant between-group differences revealed that, on average, patients in the ANI and MND groups recalled fewer words on the HVLT-R than did CU patients. Such a pattern of findings is perfectly consistent with the diagnostic characterization of the groups, and suggests, in keeping with the extant literature, that the HVLT-R might have value as a screener in and of itself. For example, the HVLT-R (total recall score), in combination with (a) the Grooved Pegboard Test or (b) the WAIS-III Digit Symbol subtest, has been identified as an adequate two-measure screening tool for HAND (Carey, Woods, Rippeth, et al. 2004). In a sample of 190 HIV-positive individuals, this two-test screening tool had a sensitivity of 78% and specificity of 85% in the former combination, and a sensitivity of 75% and specificity of 92% in the latter combination. In addition, the HVLT-R (total learning score), in combination with (a) the Stroop Colour Test and/or (b) the Stroop Colour Test and the Paced Auditory Serial Addition Test, has also been identified as part of adequate two- and three-test screening tools (Moore et al., 2012). In a sample of 200 American HIV positive individuals, the two-test screener had a sensitivity of 73% and specificity of 83%, and the three-test screener had a sensitivity of 86% and specificity of 85%. Although there is inconsistency in the literature regarding which outcome variables on the HVLT-R produce the best diagnostic results (Carey, Woods, Rippeth, et al. 2004; Moore et al., 2012), it is evident that outcome variables from this test are useful measures to include in a screener.

Returning to the current data, regarding the total symptom score, there were significantly different means in the ANI and MND groups, with the latter, on average, endorsing the presence of more symptoms. On average, the CU group endorsed the presence of fewer symptoms than the MND group. Furthermore, the HIV-D group endorsed, on average, the presence of more symptoms than did the ANI and MND groups. This particular set of findings is not surprising, given that the more severe the diagnosis, the worse the cognitive impairment, and therefore the more likely such impairments interfere with ADLs (Antinori et al., 2007), and therefore present to the

patient as a recognizable symptom. On the other hand, the CU group endorsed, on average, the presence of more symptoms than did the ANI group. This finding is unusual, given that CU participants are assumed to be symptom-free. What is possible, then, is that the symptom questions posed by the CAT-Rapid are not necessarily tapping into symptoms *specifically* and *solely* associated with HAND. Instead, these symptom questions might also be representative of occasional cognitive mishaps applicable to cognitively healthy individuals in their everyday life.

Furthermore, the unsuitability of these symptom questions for the clinical population was demonstrated through a regression model that was not a statistically good fit for the data: The model explained only 3.8% of the variance in CAT-Rapid outcome. Furthermore, each individual symptom question was not a significant predictor of overall CAT-Rapid performance. In conclusion, then, and as mentioned earlier, alternative symptom questions should be considered that elicit whether (and to what extent) the representative cognitive complaints are actually interfering with ADLs.

**Construct validity of the CAT-Rapid in the clinical sample.** Hypothesis 5 stated that, in a sample of HIV-positive participants, the correlation between performance on the paper-and-pencil CAT-Rapid word recall subtest and that on an analogous standardized paper-and-pencil neuropsychological test (HVLT-R delayed recall trial) will be significantly different from zero. This prediction was disconfirmed: There was a non-significant positive relationship between the outcome two variables.

This result might be attributable to the possibility that the CAT-Rapid is an easier test than the HVLT-R. Study 2 data presented earlier demonstrated no significant between-group differences in terms of overall CAT-Rapid performance, and significant between-group differences on the HVLT-R delayed recall trial. These latter differences are not surprising, given that the HVLT-R is more challenging than the CAT-Rapid (i.e., it requires that the participant encode and recall 12 words, whereas the CAT-Rapid's requirement is 4 words).

These findings regarding the lack of convergent validity of the CAT-Rapid word recall subtest in a clinical sample are inconsistent with findings from the IHDS (Joska et al., 2011) and NeuroScreen (Robbins et al., 2014). Regarding the IHDS, Joska et al. (2011) reported that, in a sample South African HIV-positive individuals, performance on

the IHDS word recall subtest had a statistically significant positive relationship with that on the HVLТ delayed recall trial. This same pattern of data was reported by Robbins et al. (2014); in a sample of American HIV-positive individuals, performance on NeuroScreen's word recall subtest had a statistically significant positive relationship with that on the HVLТ delayed recall trial.

**Diagnostic validity of the CAT-Rapid.** Analysis of the diagnostic validity of the CAT-Rapid proceeded across three stages: (a) preliminary analyses utilizing ROC curves; (b) main analyses addressing the hypotheses in question; and (c) post-hoc analyses exploring alternative cut-off points for the instrument.

**Preliminary findings.** Analyses from the ROC curves suggested that the CAT-Rapid only had significant discriminatory capacity in terms of sensitivity and specificity for the differential diagnosis of CU versus symptomatic HAND. Regarding specificity values, a cut-off point of 11.25 yielded a specificity of 28% across all differential diagnoses. As mentioned earlier, I selected cut-off points with a higher sensitivity value, as it is more useful in clinical settings *not* to miss any patients that might be impaired (Knight, Sherritt, Harris, Gates, & Chang, 2003). Regarding sensitivity values, a cut-off point of 11.25 yielded a sensitivity of 80%, 78%, 89%, and 100% for the differential diagnoses of CU participants from participants diagnosed with (a) any form of HAND, (b) mild HAND (ANI and MND), (c) symptomatic HAND (MND and HIV-D), or (d) HIV-D.

Although the CAT-Rapid yielded the best sensitivity value for the differential diagnosis between CU participants and those with HIV-D, the AUC value was not statistically significant. Once again, this non-significant finding is most likely attributable to extremely low power, given the small sample size of the HIV-dementia group ( $n = 4$ ). Therefore, at a cut-off point of 11.25, the tool is best at distinguishing between CU participants and those with symptomatic HAND. This finding is not surprising, given that the combined sample size for the MND and HIV-D groups is considerably better in comparison to the sample sizes of the individual groups.

Because analyses from the ROC curves only produced cut-off results in quarter increments (e.g., 10.25, 10.75), coupled with the fact that scores in these increments are unobtainable on the CAT-Rapid, I proceeded to the main analyses that explored integer

and half-integer cut-off points (e.g., 10, 10.50), as these increments are obtainable on the instrument.

***Diagnostic validity of the CAT-Rapid at the recommended cut-off score of  $\leq 10$ .*** Hypothesis 6 stated that, using the recommended cut-off score of  $\leq 10$  (Joska, 2013), the paper-and-pencil CAT-Rapid will display high sensitivity and specificity in differentially diagnosing individuals falling in the following HAND categories from cognitively unimpaired (CU) individuals: (a) all three forms of HAND (ANI, MND, HIV-D); (b) milder forms of HAND (ANI, MND); (c) symptomatic HAND (MND, HIV-D); and (d) HIV-D. This a priori prediction was disconfirmed: The CAT-Rapid displayed suboptimal diagnostic properties for all tested differential diagnoses (i.e., none of the sensitivity values for any of the differential diagnoses were at least 80%).

*Differentiating between CU and symptomatic HAND.* At the recommended cut-off score of  $\leq 10$ , the CAT-Rapid discriminated best between the CU and symptomatic HAND participants, with a sensitivity of 77% and a specificity of 49%. Compared to the IHDS (Joska et al., 2011) and the CAMCI (Becker et al., 2011), the CAT-Rapid has better sensitivity but poorer specificity.

Specifically regarding the IHDS, the diagnostic properties of this screening tool have been investigated in two South African HIV-positive samples. In a sample from Cape Town, the recommended cut-off score of  $\leq 10$  (Sacktor et al., 2005) produced a sensitivity of 45% and specificity of 79% for the differential diagnosis of CU individuals from those with symptomatic HAND (Joska et al., 2011). In a sample from Durban, the recommended cut-off score of  $\leq 10$  produced a sensitivity of 88% and specificity of 50% for the same differential diagnosis (Singh et al., 2008). Perhaps the most appropriate South African IHDS study to judge the CAT-Rapid against is that by Joska et al. (2011). Unlike the Singh et al. (2008) study, the Joska study was not of a preliminary/pilot nature, and it was conducted in Cape Town, with patients emerging from similar language, cultural, and SES backgrounds as those in the current study.

Regarding the CAMCI, in an American HIV-positive sample this tool had a sensitivity of 72% and a specificity of 98% in differentially diagnosing CU individuals from those with symptomatic HAND (Becker et al., 2011). Regarding the MoCA and

NeuroScreen, no data have been reported on the tools' ability to differentiate between CU individuals and those with symptomatic HAND.

In summary, given the importance of a high sensitivity over specificity value for clinical purposes (Knight, Sherritt, Harris, Gates, & Chang, 2003), the CAT-Rapid might be a better screening tool for symptomatic HAND (at least in South Africa) than either the CAMCI or the IHDS (no data is currently available regarding the MoCA and NeuroScreen). Furthermore, this instrument is more suitable as a screening tool in South Africa, due to the facts that (a) it is free to download and therefore requires no associated costs and, (b) it was developed in South Africa, and therefore there are no questions as to whether it is culturally appropriate for use in this country.

*Differentiating between CU and HIV-D.* In the current dataset, the next-best differential diagnosis was the CAT-Rapid's ability to discriminate between CU participants and those with HIV-D. More specifically, the CAT-Rapid displayed a sensitivity of 75% and a specificity of 49% when making this differential diagnosis. Compared to IHDS data derived from an American HIV-positive sample (Sacktor et al., 2005), the CAT-Rapid's sensitivity and specificity values are lower. Compared to IHDS data derived from a South African HIV-positive sample, the CAT-Rapid has higher sensitivity but poorer specificity regarding the differential diagnosis of interest. There are no CAMCI, MoCA, or NeuroScreen data regarding differential diagnosis of CU participants from those with HIV-dementia.

A closer examination of the IHDS's diagnostic properties in an American HIV-positive sample indicated that at the recommended cut-off score of  $\leq 10$ , this instrument demonstrated sensitivity of 80% and specificity of 57% for the differential diagnosis of CU participants from those with HIV-D (Sacktor et al., 2005). In a South African HIV-positive sample, at the recommended cut-off score of  $\leq 10$ , the IHDS demonstrated sensitivity of 70% and specificity of 65% for this differential diagnosis (Goodkin, Hardy, Singh, & Lopez, 2014).

In summary, the current preliminary findings suggest that the CAT-Rapid might not be as good a screening tool for HIV-dementia as the IHDS is, in South Africa and in the United States. However, this conclusion is preliminary, given the extremely small sample size of the HIV-D group in the current study.

*Differentiating between CU and any form of HAND.* The CAT-Rapid showed poor ability to discriminate between CU participants and those diagnosed with any form of HAND. More specifically, the CAT-Rapid displayed sensitivity of 60% and specificity of 49% when making this differential diagnosis. The IHDS (Goodkin et al., 2014), MoCA (Overton et al., 2013), CAMCI (Becker et al., 2011), and NeuroScreen (Robbins et al., 2014) all have better sensitivity and specificity in this regard.

Regarding the IHDS, at the recommended cut-off score of  $\leq 10$ , the instrument demonstrated sensitivity of 62% and specificity of 76% in discriminating between CU individuals and those diagnosed with HAND in a South African HIV-positive sample (Goodkin et al., 2014). Regarding the MoCA, a cut-off score of  $\leq 25$  yielded sensitivity of 63% and specificity of 71% when making the differential diagnosis of interest in an American HIV-positive sample (Overton et al., 2013). The CAMCI demonstrated sensitivity of 72% and specificity of 98% when making the differential diagnosis of interest in an American HIV-positive sample (Becker et al., 2011). Regarding NeuroScreen, a z-score cut-off point of  $\leq .9$  yielded sensitivity of 93.9% and specificity of 63.6% when making the differential diagnosis of interest.

In summary, the current findings suggest that the CAT-Rapid might not be as good a screening tool for HAND as the IHDS is in South Africa, and as the MoCA, CAMCI, and NeuroScreen are in the United States. However, given this tool's cultural suitability for the South African population, it might be a useful screener to use alongside the IHDS.

*Differentiating between CU and mild HAND.* The CAT-Rapid presented with the lowest combination of sensitivity and specificity when attempting to discriminate between CU participants and those diagnosed with mild HAND. This result is problematic for clinical purposes, given the higher prevalence of milder forms HAND in the cART era (Heaton et al., 2010, 2011; Joska et al., 2010, 2012; McArthur et al., 2003; Sacktor et al., 2002; Simioni et al., 2010).

Specifically, the CAT-Rapid displayed sensitivity of 59% and specificity of 49% for the differential diagnosis of interest. Compared to the IHDS (Goodkin et al., 2014), MoCA (Milanini et al., 2014), and to NeuroScreen (Robbins et al., 2014), the CAT-Rapid has poorer sensitivity and specificity in this regard. The IHDS, at the recommended cut-

off score of  $\leq 10$ , demonstrated sensitivity of 60% and specificity of 68% for the differential diagnosis in question in a South African HIV-positive sample (Goodkin et al., 2014). Regarding the MoCA, at a cut-off point of  $\leq 25$  this instrument yielded sensitivity of 72% and specificity of 67% for the differential diagnosis of interest in an American HIV-positive sample (Milanini et al., 2014). Regarding NeuroScreen, a z-score cut-off point of  $\leq .9$  yielded sensitivity of 88.9% and specificity of 62.5% when making the differential diagnosis of interest in an American HIV-positive sample (Robbins et al., 2014). To date, there are no published data regarding the CAMCI's diagnostic properties for the differential diagnosis between CU individuals and those with the milder forms of HAND.

In summary, the current findings suggest that the CAT-Rapid might not be as good a screening tool for mild HAND as the IHDS is in South Africa, or as the MoCA and NeuroScreen are in the United States. Again, despite the CAT-Rapid's unsatisfactory findings, due to its cultural suitability for the South African population, it might be a useful screening tool to use alongside the IHDS.

*Alternative cut-off scores for the CAT-Rapid.* I conducted additional diagnostic analyses to determine whether adjusting the recommended cut-off score would improve the CAT-Rapid's diagnostic properties. At a cut-off score of  $\leq 9.5$ , in comparison to the recommended cut-off score of  $\leq 10$  (Joska, 2013), the CAT-Rapid did not discriminate better between CU individuals and those with any form of HAND. In contrast, at this adjusted cut-off point, the tool's specificity was higher than that at the recommended cut-off score. However, given the fact that a better sensitivity value is more important in a clinical context, this adjusted cut-off score is not better than the recommended cut-off score of  $\leq 10$ .

At a cut-off score of  $\leq 10.5$ , the CAT-Rapid showed, in terms of sensitivity, better (in comparison to the recommended cut-off score of  $\leq 10$ ) ability to discriminate between CU participants and those with (a) any of the three forms of HAND, and (b) those with the milder forms of HAND (i.e., ANI and MND). Despite these promising results, sensitivity values at this cut-off score were still suboptimal (i.e., below 80%). This fact, coupled with the accompanying lower specificity values (in comparison to the recommended cut-off score) suggests that increasing the recommended cut-off score to  $\leq$



10.5 does not substantially improve the tool's diagnostic properties for the forms of HAND that are currently most prevalent (i.e., ANI and MND).

Lastly, at a cut-off score of  $\leq 11$ , the CAT-Rapid showed better sensitivity but poorer specificity (in comparison to the recommended cut-off score of  $\leq 10$ ), in the differential diagnosis between CU individuals and those with (a) HIV-dementia, (b) symptomatic HAND, and (c) any form of HAND. These results are promising. Furthermore, the sensitivity value resulting from the adjusted cut-off score of the CAT-Rapid (78%) shows promise for the differential diagnosis of the more prevalent milder forms of HAND. While this sensitivity is not optimal (i.e., at least 80%), it might be a useful screener in the interim period, until a screening tool that is robustly sensitive to the milder forms of HAND is available in South Africa.

***Confounders of CAT-Rapid performance.*** Because the groups were well-matched, the currently observed patterns of data were not confounded by variables such as nationality, race, home language, sex, handedness, SES, age, and current CD4 cell count at the time of testing. However, CU HIV-positive participants had completed significantly more years of education than had individuals with HAND (and, specifically, those diagnosed with MND). This pattern is consistent with previous research suggesting that lower levels of education are associated with the HAND diagnosis, and especially with HIV-dementia (Goodkin et al., 2014; Joska et al., 2011; McDonnell et al., 2014; Overton et al., 2013; Tozzi et al., 2007). One possible mechanism underlying this association is that participants with symptomatic HAND have less of a “cognitive reserve” (related to fewer years of education) to serve as a protective mechanism against neurocognitive impairment. This is a concept that has been well researched in relation to the cognitive decline that presents as part of Alzheimer's disease (Ewers, Insel, Stern, & Weiner, 2013; Roe, Xiong, Miller, & Morris, 2007; Stern, 2006, 2012).

### **Limitations and Suggestions for Future Research**

Although a priori power analyses suggested the current studies had sufficient power to detect the effects under consideration, and although the Study 2 research team screened the HIV-positive participants carefully to ensure that potential confounding

variables did not contaminate the analyses, there are still some limitations that bear consideration and that suggest caution in interpreting the data.

Regarding Study 1, I was unable to explore the effects of SES on CAT-Rapid performance, given the relatively skewed distribution of this variable (i.e., most participants were from higher SES backgrounds, Hollingshead Index 7-9). Such a finding is not unexpected, given that the study sample consisted entirely of undergraduate students from UCT. Thus, future research should investigate the effects of SES on CAT-Rapid performance, given South Africa's high levels of social inequality (Burger, Van der Berg, & Von Fintel, 2012; Spaul, 2013).

Regarding Study 2, there are several potential limitations to note. First, the smartphone version of the CAT-Rapid was not administered. This is problematic, as a lack of data on the smartphone CAT-Rapid means there is no construct and diagnostic validity evidence for a version that is perhaps more suitable for HIV-positive individuals residing in resource-limited settings. Thus, future research should investigate the psychometric properties of the smartphone CAT-Rapid in an HIV-positive South African sample.

Second, due to administration error on the paper-and-pencil CAT-Rapid in the HIV-positive sample, the time it took participants to complete the trail making test was not recorded. As a result, complete construct validity properties of this subtest were unobtainable; future research should investigate these properties.

Third, despite the fact that HIV-positive participants in the current sample were all on cART, and although this makes the sample quite an accurate representation of the population of HIV-positive individuals in contemporary South Africa, the neuropsychological performance of participants in this study might be (at least partially) attributable to the effects of the medication (Suarez et al., 2001; Joska et al., 2010; Joska et al., 2012). This is problematic, as we cannot ascertain whether construct and diagnostic validity outcomes in Study 2 are purely attributable to the HIV virus and its associated cognitive impairments.

Fourth, the uneven sample sizes across HAND categories (e.g., HIV-D group  $n = 4$ ) are likely responsible for at least some of the observed results in Study 2 (e.g., a non-significant AUC value for the differential diagnosis between CU participants and those

with HIV-D). This limitation renders all conclusions drawn from these results as preliminary. Future research should ensure equal (and larger) sample sizes across HAND categories to ensure that any observations are not tainted by disproportionate sample sizes.

### **The value of shortened paper-and-pencil neuropsychological screeners.**

Because the current data suggest that the CAT-Rapid's diagnostic properties are not optimal (i.e., at the recommended cut-off score, most sensitivity values are below 80%), I present below a brief review of alternative HAND screening measures that have provided evidence of diagnostic validity across various cultural contexts. A growing body of literature has proposed the use of short paper-and-pencil neuropsychological batteries as screeners, as these tests are already available, and do not require a high level of training to administer. Many such studies exist; however, I will provide examples of just a few recent ones.

A shortened battery (the NEU Screen; administration time  $\leq 10$  minutes) that included paper-and-pencil measures of attention and working memory, verbal fluency, and executive functioning, yielded sensitivity of 75% and specificity of 81% in the detection of neurocognitive impairment (NCI) in an HIV-positive sample in Spain (Muñoz-Moreno et al., 2013). When this measure was widened to include additional neuropsychological tests (approximately 35 minutes for completion), sensitivity and specificity were 100% and 96.3% in the detection of NCI, respectively. Another shortened paper-and-pencil battery ( $\leq 11$  minutes), which included measures of inhibition and verbal learning and memory, resulted in sensitivity of 73% and specificity of 83% in the detection of NCI in an American HIV-positive sample (Moore et al., 2012). Including two additional neuropsychological tests to the battery ( $\leq 18$  minutes) resulted in sensitivity of 86% and specificity of 87%. Additionally, a combination of a verbal learning and memory measure coupled with a psychomotor coordination measure, and a combination of a verbal learning and memory measure coupled with an information processing speed measure, resulted in sensitivities of 78% and 75% respectively in the detection of NCI an HIV-positive American sample (Carey, Woods, Rippeth, et al., 2004).

Given these positive results regarding abbreviated paper-and-pencil neuropsychological screeners, the next step for South African researchers is to compare CAT-Rapid performance and diagnostic properties to performance and diagnostic properties of these screeners (and to NeuroScreen) in this country. Doing this would determine whether these alternative screening tools might be useful in South Africa.

### **Summary and Conclusion**

There is an urgent need for a culturally appropriate and valid screening measure for HAND in South Africa. The CAT-Rapid is a screening measure developed in South Africa for use in the local HIV-positive population. It is appropriate for use in resource-limited settings in that it is brief and easy to use, and is available as a smartphone application that eliminates the need for additional administration tools.

Study 1 demonstrated, using a healthy undergraduate university student sample, that there is evidence of construct validity for both the trail making and word recall subtests of both versions of the CAT-Rapid. However, due to the significant between-administration differences, the developer should decide on one mode of administration across clinical settings. Furthermore, the CAT-Rapid was sensitive to (many of) the cognitive domains typically affected in HIV, rendering it useful for clinical (preliminary diagnostic) purposes.

Study 2 presented findings from an HIV-positive South African sample on construct and diagnostic validity of the CAT-Rapid. Analyses suggested that, in this sample, the instrument did not demonstrate evidence of optimal construct and diagnostic validity (the latter associated with the recommended cut-off score of the screening tool). In terms of diagnostic validity, at the recommended cut-off score the CAT-Rapid demonstrated the highest sensitivity in the detection of symptomatic HAND, followed by HIV-dementia, any form of HAND, and mild HAND, respectively. Overall, the CAT-Rapid's diagnostic properties were also poorer than those of the IHDS, MoCA, CAMCI, and NeuroScreen (where appropriate comparisons could be made). Increasing the CAT-Rapid's cut-off score to  $\leq 11$  improved the tool's sensitivity across HAND categories, at the expense of extremely poor specificity values.

Findings from this study have important implications for the South African clinical setting. First, the fact that the CAT-Rapid did not demonstrate strong construct validity properties in the HIV-positive sample needs to be carefully considered when interpreting the tool's diagnostic properties. Second, at the recommended cut-off score of  $\leq 10$ , the CAT-Rapid did not reach optimal (i.e., 80% or higher) sensitivity values. Thus, using the CAT-Rapid at this recommended cut-off score suggests limited suitability for the tool as a HAND screener. However, increasing the cut-off score to  $\leq 11$  made the situation appear more promising: At that cut-off score, sensitivity values were 80% and above for all differential diagnoses, with the exception of that between CU participants and those with mild HAND (specificity 28%).

An important aspect of this thesis is that it is one of the few that report on construct validity properties of a HAND screening tool. Such findings have been reported for the IHDS (Joska et al., 2011) and for NeuroScreen (Robbins et al., 2014), but are lacking for many of the other existing HAND screening tools (Kamminga et al., 2013).

A growing body of literature is demonstrating that combinations of a few different paper-and-pencil neuropsychological tests offer promise as a screening tool for HAND, especially in terms of diagnostic properties across cultural settings. Hence, the next step in South Africa is to compare the CAT-Rapid to such screening batteries, and to NeuroScreen.

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**Appendix A:**  
**Sociodemographic and Medical Questionnaire for Student Sample**



**University of Cape Town**  
**Department of Psychology**  
**ACSENT Laboratory**

HIV-Associated Neurocognitive Disorders in South Africa:  
Validation of the CAT Rapid: a smartphone screening tool

**Part A: Demographic Information**

Date of birth:

Age in years:

Race: *Black/White/Colored/Indian/Asian/Other*

Nationality: *South African/Non-South African*

Marital status: *Married/divorced/widowed/single*

Monthly household income:

Home language: *English/Afrikaans/Xhosa/Other*

Years of education completed:

Current level of study: *1<sup>st</sup> year/2<sup>nd</sup> year/3<sup>rd</sup> year/4<sup>th</sup> year*

Major(s):

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**Part B: Medical Information**

Have you experienced any of the following?

- Epileptic seizures: *YES/NO*
- Stroke: *YES/NO*
- Tumor: *YES/NO*
- Brain hemorrhaging: *YES/NO*
- Psychiatric illness: *YES/NO*  
If yes, please list conditions with which you have been formally diagnosed:

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- Traumatic Brain Injury with Loss of Consciousness: *YES/NO*
- Any other medical event(s):

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- Are you currently on psychiatric medication? *YES/NO*  
If yes, please list medications you are currently prescribed:

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- Are you currently on any other type of medication? *YES?NO*  
If yes, please list medications you are currently prescribed:

---



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- Are you currently using any drugs/alcohol? *YES/NO*  
If yes, please list the names of drugs you are currently using. For both drugs and alcohol, please describe how many times a week you are using:

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- Do you have a history of alcohol and/or drug abuse? *YES/NO*  
If yes, please list the name(s) of drug(s) and/or alcohol you have used, and how many times a week:

---



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## Appendix B: CAT Rapid Paper-and-Pencil Version

### Cognitive Assessment Tool- Rapid Version (CAT-Rapid)

**1. Symptoms-** Ask the patient the following questions exactly as they are written:

"Compared to your best:

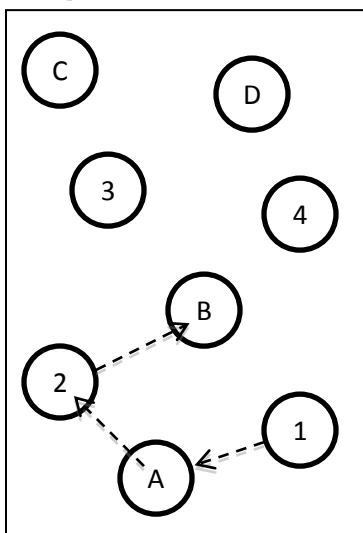
- |   |         |     |
|---|---------|-----|
| - do you often have problems remembering information?         | Y=0 N=1 |     |
| - are your hands clumsy, shaky or weak?                       | Y=0 N=1 |     |
| - have you found it hard to follow a conversation or a story? | Y=0 N=1 |     |
| - do you have trouble planning or doing daily activities?     | Y=0 N=1 | □/4 |

**Word Registration-** Give 4 words to recall (apple, watch, table, red), reading one second for each. Ask the patient to repeat them. If not correct say words again. Tell patient you will ask for all 4 words a bit later.

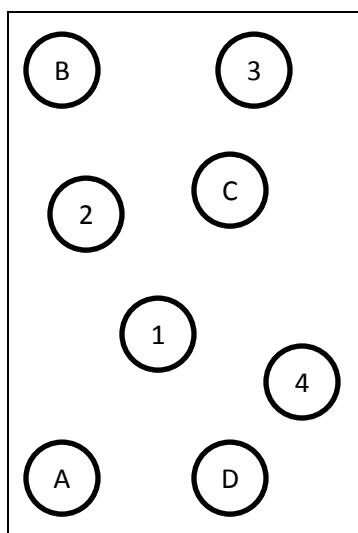
Fold →

**2. Trail-making:** Ask the patient to draw a line connecting the numbers and letters starting from the lowest number. They must switch between the letters and the numbers from start to finish in one continuous line. They must not lift the pen/pencil off the page. The example shows how to do it. They should go as quickly as they can without making mistakes.

Example



Test



Score 1 point for each correct pair of number/letter, linked in sequence:

□/4

Fold →

**3. Word recall:** Ask the patient to recall the 4 words. For words not recalled, provide a clue (for apple- "fruit", for watch- "jewelry", for table- "furniture", for red- "colour"). Score 1 point for spontaneous recall of a word and ½ for prompted recall.

□/4

Total CAT-Rapid score: Add scores for 1. – 3. together to a maximum of 12 points.

□/12

Interpretation:

>10: this score suggests that a diagnosis of dementia is unlikely. Consider another cause for symptoms or refer for further opinion or testing.

Score <10: this score suggests that dementia may be present. Confirm the diagnosis by excluding contributory causes, applying clinical judgment and performing investigations as indicated. Consider referring for further opinion or testing.

## Appendix C: Informed Consent Form for Student Sample



**University of Cape Town  
Department of Psychology  
ACSENT Laboratory**

HIV-Associated Neurocognitive Disorders in South Africa:  
Validation of the CAT Rapid: a smartphone screening tool

### 1. Invitation & Purpose

You are invited to take part in a research study about HIV-associated neurocognitive disorders in South Africa. I am a researcher from the Department of Psychology at the University of Cape Town. This project aims to validate a smartphone screening tool called “CAT Rapid” that has been developed for South Africa’s HIV-positive population. The expected duration of your participation will include two 60-minute sessions. Funding for this study comes from the National Research Foundation.

### 2. Procedures

If you decide to take part in this study, I will ask you to participate in two sessions of 60 minutes each. The sessions will be separated by a 1-day break. One session will include taking a set of paper-and-pencil neuropsychological tests. The tasks will test your attention, verbal memory, working memory and processing speed abilities.

The other session will include taking an electronic equivalent of the neuropsychological paper-and-pencil tests on a smartphone, as well as the paper-and-pencil version of the smartphone test. The questions will be about your current functioning, and tasks will be related to your attention, verbal memory, working memory and processing speed. You will also be asked to complete a questionnaire regarding demographic information and a short medical history.

### 3. **Risks, Discomforts & Inconveniences**

This study poses minimal risk to you. The main risk is that you grow fatigued throughout the testing session. However, you will be allowed to: take breaks in-between each task; choose not to answer a question or complete a task; or withdraw from the testing session at any point, with no penalty.

### 4. **Benefits**

You will not benefit directly from this study, except for gaining SRPP credits. However, the data and knowledge collected will have a positive impact on HIV-positive individuals in South Africa. If successful, the CAT Rapid will be made available for use by healthcare professionals so that patients at risk for HIV-associated neurocognitive disorders can be identified and referred for further testing by fully-trained and qualified neuropsychologists.

### 5. **Compensation**

Upon completion of the two 60-minute sessions, you will be awarded 3 SRPP points for your participation. These points can be used towards DP requirements for one of your psychology courses.

### 6. **Privacy & Confidentiality**

I will take strict precautionary measures to ensure that your personal information is safeguarded throughout the study. Your data will not be directly linked to your name, but to a unique study number. That number, but no other identifying information, will be recorded on the CAT Rapid smartphone, its equivalent paper-and-pencil test, and on the paper-and-pencil neuropsychological test battery and questionnaire. Only myself or members of the research team will have access to your information.

### 7. **Questions & Comments**

Please direct any questions or comments about this study to:

Researcher: Jade Witten  
Email: [jwitten89@gmail.com](mailto:jwitten89@gmail.com)

Supervisor: Dr. Kevin Thomas  
Telephone: 021-650-4608  
Email: [kevin.thomas@uct.ac.za](mailto:kevin.thomas@uct.ac.za)

## 8. Signatures

[Participant's name]\_\_\_\_\_ has been informed of the nature and purpose of the procedures described above including any risks involved in its performance. S/he has been given time to ask any questions and these questions have been answered to the best of the researcher's ability. A signed copy of this consent form will be made available to the subject.

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Researcher's Signature

Date

I have been informed about this research study and understand its purpose, possible benefits, risks, and discomforts. I agree to take part in this research as a subject. I know that I am free to withdraw this consent and quit this project at any time, and that doing so will not cause me any penalty or loss of benefits that I would otherwise be entitled to enjoy.

---

Participant's Signature

Date

**Appendix D:  
Debriefing Form for Student Sample**



**University of Cape Town  
Department of Psychology  
ACSENT Laboratory**

HIV-Associated Neurocognitive Disorders in South Africa:  
Validation of the CAT Rapid: a smartphone screening tool

Dear Participant,

During this study, you were asked to complete a variety of neuropsychological tasks on a smartphone application and in paper-and-pencil forms. The purpose of this study was to validate a smartphone screening tool called “CAT Rapid” that has been developed for use in South Africa’s HIV-positive population.

South Africa has the highest number of individuals living with HIV in the world. HIV-positive individuals are living longer due to treatment access, resulting in an increasing number of people who develop an HIV-associated neurocognitive disorder (HAND). This places importance on an effective screening tool that can detect HAND in HIV-positive individuals, which was the purpose of my study. The tests of processing speed, attention, working memory, and verbal memory were used, as these are the cognitive domains affected by the virus. If this tool is successful, it will be used in South African medical clinics.

If you have questions, comments, or concerns about your participation in this study, please contact me via email ([jwitten89@gmail.com](mailto:jwitten89@gmail.com)); or contact my supervisor, Dr. Kevin Thomas, via email ([kevin.thomas@uct.ac.za](mailto:kevin.thomas@uct.ac.za)) or telephone (021-650-4608).

Many thanks for your participation in my study.

Sincerely,

Jade Witten

**Appendix E:  
IsiXhosa Informed Consent Form for Clinical Sample**

**IPHETSHANA ELIQULETHE IINKCUKACHA ZOMTHATHI-  
NXAXHEBA NEFOMU YEMVUME YAKHE**

**ISIHLOKO SEPROJEKTHI YOPHANDO: Ukuvavanyela Izigulo Zengqondo Ezinxulumene Nentsholongwana kaGawulayo {okanye Screening for HIV-associated Neurocognitive Disorders (SHAND)}**

**UMPHANDI OYINTLOKO:** Professor John Joska

**IDILESI:** Department of Psychiatry and Mental Health, J-block, Groote Schuur Hospital, Anzio Road, Observatory, 7925

**Inamba yoqhagamshelwano: 021-404 2164 / 021-4042151**

Uyamenywa ukuba uthabathe inxaxheba kwizifundo zophando ezinxulumene nezo ubuthabathe inxaxheba kuzo ngaphambili eGroote Schuur. Nceda uthathe ixesha ufunde lenkcazelo ilapha, ezakucacisa iinkcukacha zaleprojekthi. Nceda ubuze abasebenzi bophando okanye ugqirha nayiphi na imibuzo, nangayiphi na ingxalenye yoluphando ongayiqondiyo. Ukuthabatha kwakho inxaxheba kungokokuzithandela kwaye wamkelekile ukuba wale ukuthabatha inxaxheba. Kwaye wamkelekile ukuba ungarhoxa nanini na koluphando, nakuba uvumile ukuthabatha inxaxheba.

**Ezi zifundo ziphehlelelwe** yiKomiti yeZenzo eziFanelekileyo kwiiNkqubo zoPhando

kwiFakhalathi yeziFundo zeSayensi kwezeMpilo kwiYunivesithi yaseKapa neKomiti yoPhando Ngabantu kwiYunivesithi yaseStellenbosch **kwaye zizakuqhutywa ngokwemigaqo nemithetho eyaBhengezwa ngaMazwe oMhlaba eHelsinki, iKomiti yeMigaqo Yokwenza Umsebenzi Ngendlela eFanelekileyo yoMzantsi Afrika kunye neyeBhunga eliPhanda ngamaChiza (iMRC).**

### **Olu phando lumalunga nantoni?**

- Olu phando luza kuqhutywa eGroote Schuur Hospital. Uphando lujonge ukuquka abantu aba150 abaphila neHIV eMzantsi Afrika. Kwaye siceba ukwenza uphando kwinani elifanayo kubantu abaphila neHIV eMelika.
- Olu phando luza kwenza udliwano-ndlebe kunye novavanyo lokuba ungayenza kakuhle kangakanani imisetyenzana yokukhumbula nokucinga (nje ngaleyo yangaphambili, kodwa imfutshane). Singathanda ukubona ukuba izixhobo ezincinci zingakwazi ukubona ukuba abantu banengxaki yenkumbulo nokucinga ngengxa yeHIV.
- Abathabathi-nxaxheba abalulungeleyo oluphando bazakucelwa ukutyikitya lefomu. Udliwano-ndlebe luza kuthatha malunga neeyure ezimbini. Uzakubuzwa umibuzo malunga nawe, unyango lwakho lweHIV kunye nempilo yakho.
- Ayinguye wonke ubani ohambela iikliniki oyakucelwa ukuba athabathe inxaxheba. Siza kufowunela abantu ababezile ngaphambili size sibabuze ukuba ngobani abangathanda ukuthabatha inxaxheba.
- Ngaphandle kodliwano-ndlebe, olu phando aluzukunikela ngempatho ekhethekileyo okanye amachiza. Ukuba kufunyanwa ingxaki yengqondo uzakuthunyelwa kwikliniki ekufutshane nawe uze ufumane unyango. Naluphi na unyango olunxulumene neHIV/AIDS uyakulifumana kwikliniki yakho yesiqhelo.

### **Kutheni umenyelwe ukuba uthabathe inxaxheba?**

- Umenywe ukuba uthabathe inxaxheba inxaxheba kuba iingxaki zenkumbulo nezokucinga kwiHIV/AIDS aziqondwa ngokupheleleyo zingcali zamayeza. Sinethemba lokwazi ngakumbi ngendlela ekhawulezileyo yokubhaqa abantu abaneHIV abaneengxaki zokucinga, ukuze sibaxilonge.

### **Luza kuba yintoni uxanduva lwakho?**

- Uzakufuneka ufike ngexesha kwityelelo lophando uze uthabathe inxaxheba ngokupheleleyo kangangoko. Oku kuthetha ukuba uyakuphendula imibuzo ngokupheleleyo nangokunyanisekileyo kangangoko. Ukuba ikhona imibuzo ongafuniyo okanye ongakwaziyo ukuyiphendula kumele utsho.



### **Ingaba uzakuzuza ngokuthabatha inxaxheba kolu phando?**

- *Uzakuzuza ngokuthe ngqo kolu phando ngendlela ezimbini – okokuqala, kuza kwenziwa uvavanyo oluntsokothileyo lwengqondo, oluza kusivumela ukuchaza size sinyange naziphi na iingxaki onokuba nazo. Okwesibini, naziphi iingxaki zenkumbulo okanye zokucinga ziza kuchazwa, okuya kusivumela ukuba sizinyange ukuba kunokwenzeka, nokuba sikunike nenkxaso oyidingayo ukuphila neHIV/AIDS.*

### **Ingaba zikhona izingozi ezikhoyo ekuthatheni inxaxheba kolu phando?**

- *Olu phando luzakwenza uzive ungazinzanga njengoko uthetha ngengxaki zempilo yengqondo. Usenokiziva uhlazekile okanye unentloni. Kwakhon, abanye abantu bavakalelwa kukuba kubhetele ukuba bangazi ngengxaki zokukhumula (zenkumbulo) okanye zokucinga.*
- *Ezi zezona ngozi ziphambili. Uze uzive ukhululekile ukuchaza indlela ovakalelwa ngayo okanye inkxalabo yakho kulo naluphi na ilunga lophando.*

### **Ukuba akuvumi ukuthabatha inxaxheba, yintoni enye onokuyenza?**

- *Ukhululekile ukuba ungathabathi nxaxheba okanye urhoxe nangaliphi na ixesha phakathi kophando. Unyango lwakho alusayi kuphazamiseka nangayiphi na indlela. Ungaqhubeka usiya kwikliniki yakho. Kuya kuba luncedo kwiqumrhu lophando ukuba usichazele isizathu sokunga thabathi nxaxheba, kodwa wamkelekile nokunganiki isizathu.*

### **Ngubani oyakubona ingxelo yakho yezempilo?**

- *Iinkcukacha ezifunyenweyo ngawe zizakuphathwa ngokuyimfihlo zize zikhuselwe. Ukuba ziya setyenziswa kushicilelo oluthile, igama lakho aluyikusetyenziswa. Ngabasebenzi bophando qha abazakubona ezinkcukacha. Ukuba kufuneka sikuthumele ekliniki ukufumana unyango, siza kubanika iinkcukacha ezifunekayo ukuze unyangwe.*

### **Ingaba uzakuhlawulwa kolu phando kwaye ingaba zikhona izindleko ezithile?**

Awuzukuhlawulwa ngokuthabatha inxaxheba koluphando kodwa iindleko zakho zohambo ziya kubuyekwezwa kutyelelo ngalunye. Umongikazi wophando uyakunikela iR150 qho ngokuza kwakho ekliniki. Akuyikubakho zindleko kuwe, ukuba uthabatha inxaxheba.

### Ingaba ikho enye into ekufuneka uyazi okanye uyenze?

- Kumelwe wazise ugqirha wakho ukuba uthabatha inxaxheba kwizifundo zophando.

**Xa kungxamisekile okanye uziva ufuna ukuqhagamshelana nomnye woogqirha bophando ungenza njalo ngokutsalela:**

**uDr John Joska kunombolo 021 404 2164**

- Usenako ukuqhagamshelana neKomiti yeZenzo eziFanelekileyo kwiiNkqubo zoPhando kwiFakhalithi yeziFundo zeSayensi kwezeMpilo kwiYunivesithi ku-021 406 6338 ukuba uneenkxalabo okanye izikhalazo ezingaphendulwanga ngendlela eyiyo ngugqirha wophando.

### Ubungqina bomthabathi-nxaxheba

Ngokutyikitya ngezantsi, Mna .....

ndiyavuma ukuthabatha inxaxheba kuphando olunomxholo othi: **Ukuvavanyela Izigulo Zengqondo Ezinxulumene Nentsholongwana kaGawulayo okanye i-Screening for HIV-associated Neurocognitive Disorders (SHAND)**

Ndiyabingqina ukuba:

- Ndiye ndafunda okanye ndafundelwa ezi zinkcukacha nalefomu yemvume kwaye ibhalwe ngolwimi endilwaziyo nendikhululekileyo lulo.
- Ndiye ndaba nethuba lokubuza imibuzo kwaye yonke imibuzo yam iphendulwe ngendlela eyiyo.
- Ndiyaqondo ukuba ukuthabatha inxaxheba koluphando **kungokuzikhethele** kwaye andinyanzeliswanga ukuthabatha inxaxheba.
- Ndisenokukhetha ukulishiya olu phando nangaliphi na ixesha kwaye andiyikuhlululwa okanye ndohlwaywe nangaliphi na indlela.
- Ndinokucelwa ukuba ndilishiye uphando ngaphambi kokuba luphele, ukuba ugqirha wophando okanye umphengululi uvakalelwa kukuba kuluncedo kum, okanye xa ndingayilandeli indlela yophando ngokwesivumelwano.

Isayinwe e- (*indawo*) ..... ngo (*umhla*)  
.....2008.

.....

**Umtyikityo womthabathi-nxaxheba**

Isayinwe e- (*indawo*) ..... ngo (*umhla*)  
.....2008.

.....

**Umtyikityo womphandi**

**Appendix F:  
English Informed Consent Form for Clinical Sample**

## **PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM**

**TITLE OF THE RESEARCH PROJECT: Screening for HIV-associated Neurocognitive Disorders (SHAND)**

**PRINCIPAL INVESTIGATOR:** Professor John Joska

**ADDRESS:** Department of Psychiatry and Mental Health, J-block, Groote Schuur Hospital, Anzio Road, Observatory, 7925

**Tel:** 021-404 2164/021-4042151

You are being invited to take part in a research project related to the one you took part in before at Groote Schuur. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. Your participation is **entirely voluntary** and you are free to decline to participate. You are also free to withdraw from the study at any point, even if you do agree to take part.

**This study has been approved by the** Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town and the Committee for Human research at Stellenbosch University **and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.**

### **What is this research study all about?**

- The study will be conducted at Groote Schuur Hospital. The study aims to include about 150 people living with HIV in South Africa. We also plan to study the same number of people with HIV in America.
- This study will perform an interview and testing of how you can perform certain tasks of memory and thinking (like before but shorter). We would

like to see whether short tools can pick up whether people have problems with memory and thinking due to HIV

- Participants who are suitable for the study will be asked to sign this form. The interviews will take about 2 hours. You will be asked questions about yourself, your HIV treatment and your and health.
- Not everyone who comes to the clinic will be asked to participate. We will telephone people who came here before and ask who would like to participate.
- Apart from the interviews, the study will not offer special treatment or medication. If a mental health problem is found, you will be referred for treatment at your nearest clinic. Any treatment related to HIV/AIDS you will also receive at your normal clinic.

### **Why have you been invited to participate?**

- You have been invited to participate, because memory and thinking problems in HIV/AIDS are not properly understood by medical science.. We hope to know more about how to quickly find out of people with HIV have problems thinking, so that we can examine and treat them.

### **What will your responsibilities be?**

- You will be required to attend the study visit on time and to participate as fully as possible. This means that you will answer questions as fully and honestly as possible. If there are questions you do not want to or cannot answer, you should say so.

### **Will you benefit from taking part in this research?**

- *You will benefit directly from the study in 2 main ways- first, a detailed mental health interview will be conducted, which will allow us to diagnose and treat any problems you may have. Second, any memory or thinking problems will be diagnosed, which will allow us to treat them if possible, but also to provide you with the assistance you need to manage with HIV/AIDS.*

### **Are there in risks involved in your taking part in this research?**

- *This study may make you feel uncomfortable as you talk about mental health problems. You may feel embarrassed or shy. Also, some people feel that is it better not to know about memory or thinking problems.*
- *These are the main risks. You should feel free to mention your feelings or concerns to any member of the study team.*

**If you do not agree to take part, what alternatives do you have?**

- You are free not to participate or to withdraw at any time during the study. Your treatment will not be affected in any way. You may continue to attend your clinic. It would be helpful for the study team to let us know why you have decided not to take part, but you are free to not give a reason.

**Who will have access to your medical records?**

- The information collected about you will be treated as confidential and protected. If it is used in a publication or thesis, your identity will remain anonymous. Only the direct study team will have full access to the information. If we need to refer you to a clinic for treatment, we will provide them with the relevant information needed to treat your condition.

**Will you be paid to take part in this study and are there any costs involved?**

You will not be paid to take part in the study but your transport costs will be covered for each study visit- The study nurse will give you R150 for each clinic attendance. There will be no costs involved for you, if you do take part.

**Is there anything else that you should know or do?**

- You should inform your family practitioner or usual doctor that you are taking part in a research study.

**In case of an emergency or if you feel you need to contact one of the study doctors you can do so by phoning:**

**Dr John Joska at tel no 021-4042164**

- You can also contact the Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.

**Declaration by participant**

By signing below, I ..... agree to take part in a research study entitled: **Screening for HIV-associated Neurocognitive Disorders (SHAND)**

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurized to take part.
- I may choose to leave the study at any time and will not be penalized or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) .....  
2008.

.....

**Signature of participant**

Signed at (*place*) ..... on (*date*) .....  
2008.

.....

**Signature of investigator**





<b>HREC office use only (FWA00001637; IRB00001938)</b>			
<input checked="" type="checkbox"/> Approved	<input checked="" type="checkbox"/> Type of review: Expedited	<input type="checkbox"/> Full committee	
This serves as notification that all changes and documentation described above are approved.			
Signature Chairperson of the HREC	<i>A. LIND</i>	Date	16/8/12