University of Cape Town

Department of Psychiatry and Mental Health

Division of Neuropsychiatry

A research dissertation submitted to the Faculty of Health Sciences, University of Cape Town, in partial fulfilment of the requirements for the degree of Master of Philosophy in Neuropsychiatry

Screening for HIV-associated neurocognitive disorders in perinatally infected youth: Validation of the CAT-rapid version 2 screening tool

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Declaration:

I, Lihle Mgweba-Bewana, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date: 19 October 2023

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Abstract

Title: Screening for HIV-associated neurocognitive disorders in perinatally infected youth: Validation of the CAT-rapid version 2 screening tool.

Objectives: There is a lack of locally validated cognitive screening tools for youth living with HIV. To test the validity of the Cognitive Assessment Tool Rapid v2 tool in screening for all forms of neurocognitive impairment in a sample of youth living with HIV in Cape Town, South Africa.

Design: We analysed the existing dataset of the neuro sub-study which was nested within the larger CTAAC study (Cape Town Adolescent Antiretroviral Cohort). The main study examined the long-term effects and outcomes of ARV treatment in 500 HIV-infected children and adolescents. HIV negative, matched controls were also included in the study. Component scores of the CAT-rapid version 1, the psychomotor speed and Luria hand sequence of the youth International HIV Dementia Scale were combined to form the CAT-rapid v2. SPSS version 28.0 was used for statistical analysis.

Methods: For the CAT-rapid v2 validation, the sample of YLWH was dichotomised according to the impaired and not impaired groups, based on their neuropsychological test scores. Impairment in this sample, relates to all levels of neurocognitive impairment. The combined tool has a total score of 20. Cross tabulations were then conducted in SPSS. The results were then entered into the medcalc.org online calculator to determine the sensitivity and specificity, positive and negative predictive values, positive and negative likelihood ratios, disease prevalence and the overall accuracy of the screening tool. A Receiver Operator Characteristic (ROC) curve was constructed to investigate the sensitivity, specificity, positive and negative predictive values of the CAT-rapid v2 in detecting all forms of neurocognitive disorder in YLWH.

Results: Statistical analyses did not detect significant between-group differences with regard to age, sex, language, or years of education. Significantly more participants in the YLWH however, had repeated at least one grade at school. Analyses detected significant between-group differences for CAT-rapid v2 total score, as well as for score in every cognitive domain except for attention. In each case, the healthy control group performed better than the YLWH group. A CAT-rapid v2 cut-off score of ≤17 yielded the best balance between sensitivity and specificity. At this cut off, the sensitivity of the CAT-rapid v2 screening tool was 69.31%, specificity was 50.35%, PPV of 49.65% and NPV of 69.90%.

Finally, we conducted a ROC analysis for the CAT-rapid v2 total score, plotted against the gold standard battery neuropsychological tests in the YLWH group only. The ROC analysis showed that at the cut off score of ≤ 17, the CAT-rapid v2 had a significantly better chance of screening for any cognitive impairment in YLWH from those with no impairment. The area under the curve was acceptable at 0.651.

Conclusion: Our study showed that the CAT-rapid v2 - at a cut off score of 17 or less – had reasonable sensitivity, however, it did not meet the generally acceptable statistical threshold in use for clinical settings. This screening tool may be useful for consideration in research settings and requires further development and validation for use in clinical settings.

Keywords: Youth, HIV, cognition, screening tool

Acknowledgements:

I would like to acknowledge:

a) My supervisors for their constant support, encouragement and dedication to the research process.
b) Ms Namhla Madini (UCT librarian), for her assistance and guidance.
c) The research participants, their parents and guardians.
d) My family and friends for their consistent and unwavering support throughout this journey.

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Abbreviations:

ART – Antiretroviral therapy

CAT-rapid – Cognitive assessment tool (rapid version)

HAND – HIV associated neurocognitive disorder

HIV – Human Immunodeficiency virus

LMIC – low- and middle-income countries

NCD - Neurocognitive disorders

NCI - Neurocognitive impairment

PLWH - People living with HIV

y-IHDS – youth International HIV Dementia scale

YLWH - Youth living with HIV

Glossary of terms:

CAT-rapid – The Cognitive assessment tool, rapid version 1 is a tool that was developed in South Africa by Joska et al. It was developed in response to the identified shortcomings of the IHDS in its current form. The tool contains a component that measures executive function and also has a series of four questions that determine the presence or absence of functional impairment.[1]

Criterion validity - an important aspect of validity testing for cross-cultural research. It refers to the validity of an instrument in comparison to its performance with that of an existing gold standard.[2]

Encephalitis – refers to an inflammatory process involving the brain tissue. It has numerous possible causes, including HIV.

HIV – The Human Immunodeficiency virus primarily attacks the host immune system, which, if untreated can result in AIDS (Acquired immune deficiency syndrome).

IHDS –The International HIV Dementia scale is a tool that is used to screen PLWH for all forms of neurocognitive impairment, including HAND.

y-IHDS – The youth International Dementia scale is a modified version of the IHDS. The YLWH is asked if they have ever failed a grade. They are also given the opportunity to practice the four words and the motor task until they can correctly do both.[3]

Mild Neurocognitive disorder - There is evidence of mild cognitive decline in one or more cognitive domains, namely: complex attention, executive function, learning and memory, language, perceptual motor, or social cognition. The deficits do not impact on activities of daily living.[4]

Major Neurocognitive disorder - There is evidence of significant cognitive decline in one or more cognitive domains, namely: complex attention, executive function, learning and memory, language, perceptual motor, or social cognition. The deficits do impact negatively on activities of daily living.[4]

Neuropsychological assessment - Involves a comprehensive assessment of an individual's cognitive function across six domains. Namely executive function, complex attention, learning and memory, executive, social-cognition, language, and motor functioning.[4]

Neurocognitive disorders – refers to a group of conditions with a prominent clinical profile of an acquired decline in baseline cognitive function.[4]

Test validity -refers to the extent to which an assessment tool actually measures what it purports to measure.[5]

Youth living with HIV – Individuals under the age of 18 years who were perinatally infected with HIV.

INTRODUCTION

Context:

The World Health organisation estimates that globally, 39 million people were living with HIV by the end of 2022 and 1.5 million of these individuals are children.[6] UNAIDS 2022 statistics quantified the current number of children between the age of 0-14 years, who are living with HIV as being 230 000.[7] The high prevalence of HIV and AIDS in South Africa has had numerous direct and indirect negative effects on children. These effects include poorer overall health, increased child headed households and poor educational outcomes.[8]

HIV-associated neurocognitive disorders (HAND) are a significant and persistent concern, amongst youth living with HIV (YLWH). The Frascati criteria, which are currently being debated, are the most widely used classification system for HAND in adults living with HIV.[9] This approach recognizes three conditions based on a spectrum of symptom severity and functional impairment. These include, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). A combination of neuropsychological testing and a functional assessment is used to classify individuals into one of these three categories. [10]

Less is known about diagnosing HAND in adolescence. Hoare et al. conducted a study wherein the HAND diagnostic criteria were applied to YLWH. [11] A comprehensive pediatric neurocognitive battery and an assessment of functional competence, was conducted in a cross-sectional study of YLWH and a HIV-negative control group. They found that the HAND criteria designed for adults was able to identify youth with cognitive impairments who did not fit criteria for HIV encephalitis (HIVE).[11] There are concerns regarding a higher positive assessment rate of milder forms of HAND when such diagnostic criteria are used.[3] There is also potential for significant false positives in the HIV negative control group.

Neurocognitive impairment in YLWH

Less is known about the nature and prevalence of neurocognitive impairment (NCI) and neurocognitive disorder (NCD) in YLWH in comparison to adults living with HIV. [12] This relates to the paucity of NCD literature in this population, and the absence of consensus diagnostic criteria and validated screening tools to assess NCD in YLWH. [3]

Furthermore, diagnostic challenges related to utilizing the Frascati criteria for milder forms of NCD are worth considering in this population. [13] Some of these diagnostic challenges relate to other aspects that have a negative impact on cognitive function of people living with HIV. These include low education levels, poor socioeconomic conditions and comorbid conditions. [14] Additionally, there are in utero maternal health factors, substance use, malnutrition and chronic ill health, which impacts the cognitive profile of the growing child living with HIV. [13]

Perinatally acquired HIV, results in a neurocognitive profile that is similar to the one that is found in adults living with HIV. A recent meta-analysis identified working memory, and executive function as the main domains affected in YLWH. [15] Early insults to the developing brain can result in significant scholastic difficulty for children as they mature. Neuroimaging work by Hoare et al. found that initiation of ART after the neuronal development phase of the second year of life was associated with white matter alterations (increased regional radial diffusion suggestive of myelin loss). [16] Early identification and intervention is thus an important strategy to mitigate the neurodevelopmental impact of perinatally acquired HIV infection. [17] In the event where this early stage is missed, it becomes more prudent in high prevalence and low resourced areas to initially identify the most impaired youth.

Screening versus assessment.

Screening is a process for determining the possible existence of a particular problem. Conversely, an assessment is a process used for “defining the nature of that problem, determining a diagnosis, and developing specific treatment recommendations for addressing the problem or diagnosis."[18]

There are advantages and disadvantages to the use of either of these tools. In the context of diagnosing NCD in youth, a full assessment would entail the following: a neuropsychological assessment battery; a thorough physical and neurological examination and a functional assessment for each YLWH.[19] In our resource constrained context, this would not be feasible and the majority of the youth who urgently need this kind of assessment would not receive it.

A screening tool is comparatively inexpensive, quick to complete and can be administered by any health professional.[20] The main disadvantage of screening tools is the risk of a high false positive rate.[21] This implies that unimpaired individuals may screen positive whereas they are not impaired on assessment. This may result in increased anxiety for the affected individual, as well the need for expensive further investigations.[21] One method of mitigating this potential anxiety is through the addition of a script to the tool as a means of explaining the instructions further to participants.[22] Additionally, better tools could be developed with revised screening criteria.

The overall benefit of identifying people who are indeed impaired and referring them for further assessment and formal diagnosis, is greater than the potential harm of falsely identifying individuals as being impaired when they are not.[23]

Screening tools for cognitive impairment in YLWH: Systematic search

The current gold standard for assessment of NCI in YLWH is a neuropsychological assessment battery that assesses various neurocognitive domains. [3] Additionally, a thorough collateral history and treating team discussion, completes the comprehensive assessment. These neurocognitive domains include executive function, memory, language, visuospatial, processing speed and general intellectual functioning. [24] Neuropsychological assessment batteries are time consuming and require trained neuropsychologists to administer.[25]

Screening tools for cognitive impairment PLWH, generally have higher sensitivity for detecting more severe forms of impairment.[26] This may lead to an overestimation of the true prevalence of all forms of HAND. Furthermore, these tools are less able to pick up milder forms of the condition (ANI and MND), especially if lower cut off scores are utilized.[27] Once a screening tool has been developed, it is vital to validate that tool in different contexts and population groups.[28]

There is currently a paucity of HAND literature in YLWH. Related to this scarcity is the absence of consensus HAND diagnostic criteria and validated screening tools for YLWH [3]. In order to ascertain what is currently known about cognitive assessments in YLWH, a systematic literature search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram (PRISMA) statement [29].The PICOS method was used to determine the research question which was: “What are the cognitive assessment tools that have been used to assess cognitive impairment in perinatally HIV-infected youth compared to HIV-negative controls?”

Eligibility criteria. Titles, abstracts, and full texts were assessed for inclusion by one reviewer (LM). The following eligibility criteria were applied: HIV positive youth (18 years and younger) with cognitive impairment, studies published between 2010-2021.

People older than 18 years with cognitive impairment, imaging studies, duplicate studies, other psychiatric conditions were excluded.

Search strategy. We conducted a systematic search across three databases, namely PUBMED, APA PsycINFO and Scopus. The initial systematic search yielded 538 articles. After the application of the eligibility criteria, eighteen studies remained. Three of the excluded studies met our inclusion criteria but were systematic reviews and are thus reported upon separately. (See Appendix B)

Results of the systematic search. Fourteen out of the eighteen included studies were conducted in LMIC. Seventeen of these studies had used a full neuropsychological battery and only one of them primarily used a screening tool, namely the y-IHDS [30]. The findings from the other studies in the literature search showed that YLWH in general, performed poorly in cognitive tests when compared to age matched HIV uninfected controls. The neuropsychological batteries that were used mainly contained tests that assessed memory, executive functioning, processing speed and general intellectual functioning (IQ). The Weschler Intelligence scale for children was frequently used for the IQ testing aspect. The detailed outline and analysis of the systematic search is included as Appendix B.

Several cognitive screening tools have been studied and validated in an adult population in different settings and diagnostic categories. In the context of HIV, some of the tools that have been trialled include the International HIV dementia scale (IHDS) [31]; Mini Mental state examination (MMSE) [32]; Montreal Cognitive assessment (MOCA) [33]; Simioni symptom assessment [34] and the cognitive assessment tool-rapid version (CAT-rapid). [1]

A study by Joska. et al compared the diagnostic sensitivity and specificity of the above tools against a full neuropsychological battery. Furthermore, they assessed the scores of a combined IHDS assessment tool and the CAT-rapid minus the four-word recall component, resulting in a total score of 20 for the combined tool. [1] The rationale for combining the tool was based on the recognized shortcomings of the IHDS. The IHDS does not test executive functioning and this cognitive domain is known to be adversely affected by HIV. The results of the combined screening tool markedly improved the sensitivity and to a lesser extent the specificity (89% and 82% respectively), at a cut off score < or = 16 in screening for HIV dementia in adults.[1] Similarly, a Thailand based study by Chalermchai et al. found the addition of a Trails A component to the IHDS at a cut-off score ≤ 10, significantly increased the sensitivity of the screening tool from 53.3 % to a net sensitivity of 86 % .[35]

The Frigati et al. study incorporated the y-IHDS, to assess for multisystem impairment in South African YLWH. It showed a significant proportion of uninfected youth, screened positive for cognitive impairment (45.3%).[30] This suggests that the y-IHDS over-estimates the true prevalence of NCD as evidenced by the high false positive rate. It also highlights the importance of taking into account confounders that are common to both the control and participant group.[30]

The reviewed studies showed consensus in consistently finding that YLWH had poorer neuropsychological testing outcomes compared to their age matched, HIV negative peers. This is a concerning finding as most of the adolescents were on an adequate ART regimen for at least six months. This highlights the complex and important role of other biopsychosocial factors as contributors to cognitive impairment in this population group.[36]

Ideally, cognitive screening tools would have a high sensitivity and specificity. In real life clinical settings, this is not often achieved. For example, the y-IHDS was found to have good sensitivity 94% of and poor specificity of 24% in a cohort of YLWH in South Africa.[3] Additionally, the ideal screening tool has a high positive predictive value (PPV) and a high negative predictive value (NPP). The low PPV (44.95%) and high NPP (85.37%) of a South African y-IHDS validation study, highlights the need for improvements to enhance the y-IHDS as a stand-alone cognitive screening tool. [3]

A comprehensive neuropsychological battery is the current gold standard for quantifying the extent of cognitive impairment in YLWH. [3] In resource constrained settings, it is neither practical nor feasible to perform these assessments on all YLWH. Brief, locally validated and easy to administer screening tools are thus needed. This ensures appropriate referral of affected youth, for further screening and comprehensive testing.[3]

Ethical considerations

The larger CTAAC study (including the neuro sub-study) received ethical approval from the Human Research Ethics Committee (HREC) of the UCT's Faculty of Health Sciences (HREC REF: 051/2013). Parents/caregivers gave consent for themselves and for their children. Children signed assent forms for voluntary participation. Ethics approval for this MPhil was also obtained (HREC ref: 137/2022). A copy thereof is attached at Appendix D.

Appropriate details were explained to the minor participants. All demographic information, test scores, and any other data collected were kept strictly confidential. This MPhil was an analysis of data that has already been collected in the neuro sub-study. Confidentiality was maintained during the capturing and analysis phase. There was no direct contact with any of the participants and no identifying data of participants was used.

Chapter 2:

Publication ready manuscript

Manuscript title page:

Screening for HIV-associated neurocognitive disorders in perinatally infected youth: Validation of the CAT-rapid version 2 screening tool

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Declarations:

• Conflicts of interest/Competing interests (include appropriate disclosures) -Nil from me.

• Ethics approval -Obtained from the Human research ethics committee, University of Cape Town.

• Consent to participate -all participants gave assent, caregivers/parents gave consent

• Consent for publication -Not applicable

• Availability of data and material (data transparency) -not publicly available

• Code availability -Not applicable

• Authors' contributions & approval of texts:

1.Lihle Mgweba-Bewana – Dr Mgweba-Bewana developed the concept for the paper and contributed to the conceptualisation and design of this article. She was also responsible for capturing the component scores for the data analysis. She worked on the data analysis with Dr Phillips. She was responsible for the write-up of the final manuscript and for submission to the journal, and she approved the final manuscript as submitted. Dr Mgweba-Bewana will also be the corresponding author for this article and will address any reviewer comments received. Dr Mgweba-Bewana did not receive any funding towards the completion of her MPhil thesis, which this paper forms a part of.

2.Nicole Phillips: Dr Phillips contributed to the conceptualisation and design of this article. She conducted the statistical analysis of the captured data. Dr Phillips critically reviewed the manuscript and made relevant changes prior to submission to the journal. Dr Phillips has no disclosures to make.

3. John Joska – Professor John Joska contributed to the conceptualisation and design of this article and critically reviewed the statistical methodology and results. He also read, edited and approved the final manuscript. Prof Joska has no disclosures to make.
4.Jackie Hoare – Prof Jackie Hoare contributed to the conceptualisation and design of this article, critically reviewed the statistical methodology and outcomes. She also read, edited and approved the final manuscript. Prof Hoare has no disclosures to make.

Funding – This paper forms part of an MPhil degree and thus not funded. The main CTAAC study was supported by Eunice Kennedy Shriver National Institute of Child Health and Human Development under grant R01HD074501.

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Introduction

Universal access to Antiretroviral therapy (ART) has been established, however, Neurocognitive impairment (NCI) remains a huge challenge for youth living with HIV (YLWH) [37]. HIV-associated Neurocognitive Disorders (HAND) in YLWH is an under-researched aspect of HIV research globally and even more so in Low-and-middle-income countries (LMIC) [38]. Undiagnosed HAND has significant socio-economic and functional implications for the YLWH who is growing in age [39]. Due to resource constraints and issues with the availability of local norms, it is not feasible to conduct full neuropsychological testing batteries on all YLWH. It is thus important to develop and validate brief screening tools in our local context.

Additionally, in poorly resourced settings such as South Africa, it may be prudent to use screening tools as a diagnostic aid, especially when the tool can be administered and interpreted by any allied healthcare professional and appropriate actions initiated, such as referral. Referral for formal neuropsychological testing could then be reserved for more complex cases that require additional expert input given the limited access to neuropsychological testing in LMIC.[40]

The cognitive assessment tool (CAT-rapid V2) is a novel, brief, cognitive screening tool that includes an item to assess executive function by means of a mini-trails test (appendix A). It was developed in South Africa, in response to the need to develop a brief HAND screening tool with a functional symptom question component and a measure of executive function in adults [1]. Version 1 of the tool has four parts, namely a four-question component to screen for symptoms of cognitive impairment; four-word registration (verbal learning component); a mini trail-making test and recall of the four words (appendix A). Each of the four components of the scale have a total of four points. The maximum total score is thus 16. At a cut-off score of 10 or less, the CAT-rapid v1 was able to screen for major NCD due to HIV (HAD), with a sensitivity of 94.44% and a specificity of 52% in a group of 156 adults living with HIV [1].

The y-IHDS has been validated in the South African context for use in YLWH. The y-IHDS demonstrates good sensitivity, however, it lacks the inclusion of a measure to assess executive function. A meta-analysis by Phillips et al. identified working memory, and executive function as the main domains affected in YLWH.[15] It is thus important for cognitive screening tools developed for use in this population group, to contain a measure to screen for executive function.[15]

There are numerous benefits of a validated cognitive a screening tool. It increases the available tools at our disposal for conducting brief, cognitive screening.[41] Such tools are vital in our resource constrained context.[42] The y-IHDS screening tool for example, does not require specialist training to conduct and takes approximately 10 minutes to administer and score.[3] This means that health professionals across the spectrum are able to administer the tool in their various clinical settings.[42]

Screening in adolescence is important for initiating appropriate and timeous scholastic interventions such as additional academic support in the form of remedial classes and where necessary, referral to a special needs school. [43]Early diagnosis also affords the opportunity to review ART and related therapies, to choose the most neuroprotective regimen with the least likelihood of long-term neurocognitive sequalae.[44] It also assists the parents and caregivers with personal planning and clarity regarding the adolescent's future prospects as they transition to adulthood.[45]

Objectives

The objective of this study was to validate an adapted version of the CAT-rapid version 2, which combines the first version with certain elements of the y-IHDS, in a sample of YLWH in Cape Town, South Africa.

Methodology:

Study population

The primary and sub-study from which the data are derived has been outlined and detailed elsewhere.[3] In summary, the larger Cape Town Adolescent Antiretroviral Cohort (CTAAC) research program, in which the sub-study is nested, aimed to investigate the long-term effects and outcomes of ARV treatment in HIV-infected youth in Cape Town. The CTAAC neuro sub-study, included two hundred and forty-nine (249) youth between the ages of 9 - 12 years from the Cape Town area and were recruited via community clinics. A full medical history screening, laboratory blood tests and demographic assessments were completed as part of their routine medical examination at the centre or clinic which they are attending. The recruiters of the larger study matched participants (HIV-infected and controls) based on age, ethnicity, sex, and socioeconomic background in as far as it was possible, prior to enrolment. Out of the total sample, 44 participants were HIV-uninfected controls. Two hundred and three (203) participants were vertically-infected with HIV and were stable on ARV treatment for at least 6 months prior to their study enrolment. Parents gave full consent for their child's participation in the main and sub-study. Children signed an assent form to give their own permission for participation. Ethical approval was obtained from the University of Cape Town's Faculty of

Health Sciences research ethics committee for both the main study and sub-study (HREC REF: 051/2013) and the current analysis (HREC ref: 137/2022).

Measures

All the adolescents who were enrolled for the neuro sub-study, completed a comprehensive neuropsychological test battery, the y-IHDS and the CAT-rapid version 1. The neuropsychological test battery was collated by a team of neuropsychologists and neuropsychiatrists who were the principal investigators (PI) of the neuro sub-study. The neuropsychological battery measured cognition across a wide range of domains including: general intellectual functioning, attention, working memory, visual memory, verbal memory, language, visual spatial ability, motor coordination, processing speed and executive function.

The neuropsychological tests included, among others: the Wechsler Abbreviated Scale of Intelligence; the Digit Span, Symbol Search, and Digit Symbol-Coding subtests of the Wechsler Intelligence Scale for Children; the Inhibition and Fingertip Tapping subtests of the NEPSY; and the Children's Colour Trails Test. The full list of completed tests can be found in the paper by Hoare et al.[46]

The test battery was administered by trained neurotechnicians who were fluent in isiXhosa, the predominant language of the participants, and was scored and interpreted by the PI.

Researchers from the larger study recruited and telephonically contacted the parent/caregiver of each potential child/adolescent participant to schedule medical examinations. Each participant’s HIV status was confirmed via a HIV rapid screening test. All the medical procedures were conducted at the Research Center for Child and Adolescent Health (REACH) at Red Cross War Memorial Children’s Hospital, Cape Town. The sub-study comprised of one session, which took place in the Department of Psychiatry and Mental Health of the University of Cape Town at Groote Schuur Hospital (GSH). At this session, after informed consent and assent were obtained, the children and adolescents completed the neuropsychological test battery.

The current study utilised the current version of the CAT-rapid which has not yet been translated into IsiXhosa, therefore this study does not include the IsiXhosa validation.

During the data analysis stage of the sub-study, the authors applied the youth HIV-associated neurocognitive disorder diagnostic criteria to each participant's neuropsychological profile to screen for HIV-associated neurocognitive disorders. [11] Each participant was classified as having either a major neurocognitive disorder (major ND), minor neurocognitive disorder (minor ND), or no impairment (no ND). After the completion of the neuropsychological tests, a behavioural interview was conducted. The behavioral interview included questionnaires that assessed mental health, overall functioning and psychosocial risk. Measures were outlined in a previous study.[47] This study involved secondary analysis of the collected data. There was no direct interaction with study participants.

A previous study by Hoare J. et al had assessed the cognitive the performance of YLWH, compared to established international norms.[11] The Hoare et al. study, thus began to address the challenges with YLWH versus HIV negative controls' scoring, when compared to European scores wherein these assessment tools were originally developed.[11]

Data Analysis

During the data analysis stage of the sub-study, the authors applied the youth HIV-associated neurocognitive disorder diagnostic criteria[11] to each participant's neuropsychological profile to screen for HIV-associated neurocognitive disorders.

Prior to commencing with statistical analysis, the captured data was double checked by two of the authors independently (LM and NP), for any errors in the data capturing process. Two participants had not completed a significant portion of the neuropsychological tests and were thus not included in the final analysis. We captured all the component scores from the CAT-rapid version 1, and the motor speed and psychomotor speed components of the y-IHDS. These component scores combined, formed the CAT-rapid v2 which has a total score of 20. The cognitive composite domain scores used were calculated according to the method described above. Finally, the neuropsychological test battery scores were exported into SPSS (version 28, Armonk, IBM).

In the sub-study, data from the test battery, was used to create ten separate composite cognitive domains: general intellectual functioning, attention, working memory, visual memory, verbal memory, language, visual spatial ability, motor coordination, processing speed and executive function. To determine the statistical strength of each cognitive domain, Cronbach's alpha tests were run to determine internal consistency within a specific domain. Only the total scaled scores of the tests, and/or subtests were used, for each of the individual neuropsychological tests. A Cronbach's alpha value of 0.7 was deemed high and considered as a good indication of inter-relatedness between the tests. Further details on this method can be found in the paper by Phillips et al.[3]

A stepwise approach of analysing the data was followed. The approach is modelled upon the original y-IHDS validation study, from which this study is based [3]. Analysis concerning the neuropsychological performance of this sample was completed using SPSS 28.0. The majority of the variables were not normally distributed as determined by a Shapiro-Wilk test. We did not exclude any outliers during the analysis.

Four steps were followed in the analysis:

1) We applied the youth HNCD diagnostic criteria[11] to each participant profile in order to ascertain the presence of any NCD and to further classify each participant as either having major, minor or no NCD.

2) For the CAT-rapid v2 validation, the sample of YLWH was dichotomised according to the impaired and not impaired groups as above. Impairment in this sample, relates to all levels of neurocognitive impairment. Impaired YLWH were coded as 1 and not impaired YLHIV were coded as 0. Cross tabulations were then conducted in SPSS for different cut-offs in increments of one, the range beginning at a score of 15 to 18. [3]

Within the inferential analyses, bivariate correlational analyses using the Spearman rho's co-efficient for non-normally distributed data were conducted (Table 2). This was done to determine the strength of association between the CAT-rapid v2 total score and scores within each composite cognitive domain.

3) Using these classifications that are based on the correlations between the composite scores and the total CAT-rapid v2 total score, we created the cross-tabulations. The results from the cross tabulation were then entered into the medcalc.org online calculator to determine the sensitivity and specificity, positive and negative predictive values, positive and negative likelihood ratios, disease prevalence and the overall accuracy of the screening tool (https://www.medcalc.org/calc/diagnostic_test.php). The results of the cross tabulation are contained in Table 3.

We subsequently examined the ability of the CAT-rapid v2 (at cut-off scores of 19,18, 17 and 16) -where in each case a score at or below the cut-off indicated impairment- to discriminate any form of ND (major or mild) and non-impaired participants. We then reviewed all the results at the different cut off scores to see the sensitivity and specificity of the tool.

4) Finally, we conducted a Receiver Operating curve analysis (ROC analysis) for the CAT-rapid v2 total score, plotted against the gold standard battery neuropsychological tests in the YLWH and control group for major HNCD, minor NCD and all HNCD.

Results

Table 1 summarises the demographic and clinical characteristics of the YLWH and the HIV negative control group, in order to provide an overview of the sample. There were no significant between-group differences with regard to age, sex, language, or years of education. Significantly more participants in the YLWH however, had repeated at least one grade at school. There were significant between-group differences for CAT-rapid v2 total score, as well as for score in every cognitive domain except for attention in the full battery. In each case, the control group outperformed the YLWH group. A frequency count of the number of YLWH who were cognitively impaired, at a cut off score of 17, showed that 18 out of the 44 controls scored at or below 17 (40.9%). It was also found that 123 out of 140 YLWH scored at or below 17 on the CAT-rapid v2 screening tool (60.6%).

Table 2 presents the correlation between the composite cognitive domains and the CAT-rapid v2 total score. The CAT-rapid v2 was significantly, positively associated with all of the cognitive domains, except for attention. A CAT-rapid v2 cut-off score of ≤17 yielded the best balance between all of the validity statistics, especially sensitivity and specificity, as depicted in table 3. The ROC analysis showed that at the preferred cut off score of ≤ 17, the CAT-rapid v2 had a significantly better chance of screening for any cognitive impairment in YLWH from those with no impairment (see figure 1). The area under the curve (AUC) was acceptable at 0.664, $p = 0.000$

Table 1: Summary of sample demographic and neurocognitive characteristics

Characteristic:	**Variable**	**HIV-infected (n = 203)**	**Controls (n = 44)**	**t**	**p**	**ES[f]**	**95% CI**
Demographic	Age: M (SD)	10.39 (.88)	10.38 (1.09)	-0.05	.957	-0.011	-0.31 to 0.29
	Sex: male/female	100/103	20/24	0.46	.649	0.08	-0.13 to 0.35
	Home language: isiXhosa/Other	184/19	42/2	1.04	.301	0.143	-0.04 to 0.14
	Repeated any grades: yes (%)	120 (59)	18 (40)	-2.22	.027*	-0.365	-0.34 to 0.02
	Highest grade passed[a]: M (SD)	3.21 (1.12)	3.39 (1.35)	0.93	.356	0.154	-0.20 to 0.56
Clinical	VABS[b]: M (SD)	95.19 (22.95)	95.23 (11.14)	0.02	.991	0.002	-7.03 to 7.11

Characteristic:	**Variable**	**HIV-infected (n = 203)**	**Controls (n = 44)**	**t**	**p**	**ES[f]**	**95% CI**
	CBCL[c] Competence: M (SD)	37.70 (7.77)	41.16 (7.91)	2.65	.009**	0.444	0.89 to 6.05
	CAT-rapid V2	9.55 (2.09)	10.36 (1.52)	2.45	.015	0.41	0.16 to 1.47
	CD4 count: mean (SD)	952.66 (496.45)	N/A	N/A	N/A	N/A	N/A
	Viral load[e]: suppressed (%)	117 (65)	N/A	N/A	N/A	N/A	N/A
Cognitive	Cognitive domains: means (SD):						
	General intellectual function	-.54(.78)	.00(.79)	-4.18	.001***	0.691	0.29 to 0.80
	Executive function	-.48(.67)	.01(.59)	-4.42	.001***	0.744	0.27 to 0.70
	Motor coordination	.02(.99)	.00(.91)	0.13	.862	-0.02	-0.35 to 0.29

Characteristic:	**Variable**	**HIV-infected (n = 203)**	**Controls (n = 44)**	**t**	**p**	**ES[f]**	**95% CI**
	Attention	-.39(.92)	.00(.92)	-2.55	.013*	0.424	0.08 to 0.69
	Working memory	-.35(.89)	0.00(1.00)	2.32	<.001***	0.385	0.29 to 0.69
	Visual spatial ability	-.52(1.26)	0.00(.84)	-2.62	022*	0.434	0.05 to 0.65
	Visual memory	-.49(.87)	-0.0(.98)	-3.31	.000*	0.55	0.19 to 0.77
	Language	-.38(.102)	-0.0(1.00)	-2.20	.028*	0.374	0.04 to 0.71
	Verbal memory	-.56(.67)	.00(.68)	-5.02	.009**	0.834	0.13 to 0.91
	Processing speed	-.56(.63)	-0.01(.68)	-5.02	<0.001*	0.819	0.35 to 0.78

NOTES: This table is adapted from Phillips et al with permission. a: number of years of completed formal schooling. b: Vinelands Adaptive Behaviour Scale – II;

Characteristic:	**Variable**	**HIV-infected (n = 203)**	**Controls (n = 44)**	**t**	**p**	**ES[f]**	**95% CI**

composite behaviour score presented here. c: Child Behaviour Checklist; Total Competence subscale score presented here. d: Youth - International HIV Dementia Scale. e: For VL 117 HIV-infected participants were suppressed with 64 being unsuppressed and 22 having missing VL data from the lab. f: Hedge's g calculated for groups with different sample sizes. *p < .05. **p < .01. ***p < .001.

Table 2: Correlations of CAT-rapid V2 scores with neuropsychological gold standard test measures within the YLHIV (N = 203) versus controls (N=44).

Correlation of CAT-rapid V2 raw	**Spearman Rho**	**p-value**
General intellectual function	0.249	<0.001
Attention	0.057	0.376
Motor coordination	0.321	<0.001
Visual memory	0.270	<0.001
Verbal memory	0.410	<0.001
Working memory	0.275	<0.001
Language	0.260	<0.001
Visual-spatial ability	0.339	<0.001
Processing speed	0.386	<0.001
Executive function	0.458	<0.001

NOTE: Nonparametric bivariate correlations were conducted because 67% (165 out of 244) of all variables were not normally distributed according to the Shapiro-Wilk test of normality. Correlation co-efficients are within the low to medium range (0.2-0.4).

Table 3: Sensitivity and specificity of the CAT-rapid v2 for all forms of cognitive impairment (CI) at various cut-off points for the HIV group only (N =203).

Cut-off point	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**PLR**	**NLR**	**Disease prev**	**Accuracy**
All NCD ≤ 19	99.01%	2.80%	41.84%	80.0%	1.02	0.35	41.39%	42.62%
Major NCD ≤ 19	99.01%	2.80%	41.84%	80.0%	1.02	0.35	41.39%	42.62%
Minor NCD ≤ 19	98.95%	2.80%	40.34%	80.0%	1.02	0.38	39.92%	41.18%
All NCD ≤ 18	90.10%	16.08%	43.13%	69.70%	1.07	0.62	41.39%	46.72%
Major NCD ≤ 18	100%	16.08%	4.76%	100%	1.19	0.00	4.03%	19.46%
Minor NCD ≤ 18	89.47%	16.08%	41.46%	69.70%	1.07	0.65	39.92%	45.38%
All NCD ≤ 17	**69.31%**	**50.35%**	**49.65%**	**69.90%**	**1.40**	**0.61**	**41.39%**	**58.20%**
Major NCD ≤ 17	66.67%	50.35%	5.33%	97.30%	1.34	0.66	4.03%	51.01%
Minor NCD ≤ 17	69.47%	50.35%	48.18%	71.29%	1.40	0.61	39.92%	57.98%

Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR	Disease prev	Accuracy
All NCD ≤ 16	55.45%	69.93%	56.57%	68.97%	1.84	0.64	41.39%	63.93%
Major NCD ≤ 16	66.67%	69.93%	8.51%	98.04%	2.22	0.48	4.03%	69.80%
Minor NCD ≤ 16	54.74%	69.93%	54.74%	69.93%	1.82	0.65	39.92%	63.87%

NOTE: Shaded rows indicate the cut-off score with the best sensitivity values. PPV = positive predictive value reflects the proportion of positive results that are true positives; NPV = negative predictive value reflects the proportion of negative results that are true negatives; PLR = positive likelihood ratio; NLR = negative likelihood ratio; Disease Prev = Disease prevalence

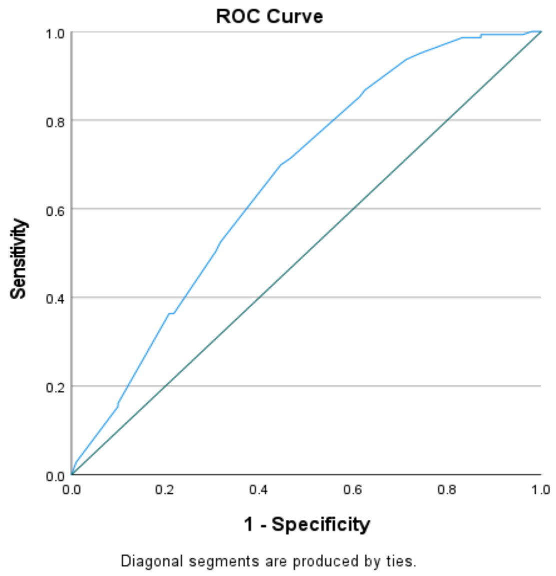


Figure 1. Area under ROC Curve = 0.664, p= 0.000 for all forms of HNCD.

Receiver operating curve of the total CAT-rapid v2 scale compared to a battery of neuropsychological tests in the YLHIV group only. Standard error (SE) 0.036. Confidence interval 0.593 - 0.734. Receiver operating curves (ROCs) were constructed based on the cut-off score which yielded the best balance between all the validity statistics.

Discussion

The current study aimed to validate the CAT-rapid v2, as a cognitive screening tool in YLWH. Our analyses found that at a score of 17 or less (out of 20), the tool had reasonable sensitivity (69.71%) but low specificity (50.35%) in screening for all forms of HNCD. Similar validation statistics were noted for major and minor Neurocognitive Disorder. The NPV (69.90%) is of particular importance for low resource settings where human and other resources are limited and suggests that this tool could be beneficial in low resource contexts with high HIV prevalence.

Our study of YLWH had a lower sensitivity and specificity at the same cut off score of 17, compared to the initial CAT-rapid study in adults which achieved a sensitivity of 59.22% and specificity of 64%.[1] A possible explanation for this difference is that our participants were still developing and maturing, given their age range (9-12 years) at the time of testing. The prefrontal cortex and particularly executive function, are some of the last brain areas to reach maturity, in late adolescence and early adulthood.[48]

Our study findings showed that our YLWH sample had a higher prevalence of all forms of HAND than what has been reported in similar LMIC settings.[49] A number of factors could account for this finding. Firstly, the tool itself has a lower sensitivity (69.71%) which is lower than generally recommended thresholds for a clinically useful screening tool. Secondly, participant related factors that include poverty, malnutrition, and lack of stimulating home environments, have a negative effect on cognitive and other aspects of development.[50]

The high prevalence (40.9%) of HIV negative control group youth who screened at or below 17 is also notable and significant. This finding may point to the broader socioeconomic and food insecurity challenges faced by a high number of South African children, irrespective of their HIV status.[50] South African children are at increased risk of experiencing and being exposed to trauma,[51] related to living in lower socioeconomic environments where crime rates are higher than in higher socioeconomic environments. These environmental factors, coupled with low mental stimulation and poverty, place South African children at greater risk of developmental delay. These factors result in general low-test performance as opposed to impairment per se.

In terms of the performance of the CAT-rapid v2 screening tool, at a cut off score of equal to or less than 17, the overall disease prevalence of all forms of HNCD was 41.39%. This is in keeping with the estimated prevalence of all forms of NCD (45.35%) that has been found by Hoare J. et al.[11] The prevalence of major HNCD (4.03%) and minor HNCD (39.92%) is also comparable to what has been found in the literature. [52] The relatively low prevalence of major NCD could be related to the protective benefit of ART, as all the participants were on treatment at the time of the study. Current HIV treatment guidelines recommend universal ART for all children and youth living with HIV, regardless of their immunological status.[53]

Our YLWH sample had a greater likelihood of an underlying HAND on this screening tool. In such scenarios, attempts should be made to minimize the rates of false negatives when screening for HAND. A high false negative result on a screening tool may miss correctly detecting YLWH with true impairment. Conversely, reducing the number of false positives is also important in low resource settings such as South Africa. This would minimise the need to do lengthy and time-consuming neuropsychological batteries on youth who may not require such assessments. The CAT-rapid v2 screening tool in its current form, did not have a high enough sensitivity and specificity for us to recommend it for use in clinical settings. A high sensitivity is generally recommended for a screening tool for its clinical utility, although no specific cut-offs have been published to date. This tool does however, add to the knowledge base in this area and can be used for future research. This tool or aspects thereof, could serve as a stepping stone towards developing screening tools with greater sensitivity and specificity.

We identified two main of limitations to our study. Firstly, the use of the CAT-rapid cognitive screening tool is novel. There are thus currently no other studies to compare our findings to. Secondly, higher numbers of YLWH compared to HIV negative controls were included in the analysis. The two groups were however, well matched and the statistical analysis used was not impacted by variances between the groups. IsiXhosa translations are not yet normed and validated but in the context of low resources and predominant use of western developed measures, we are limited. The original study Neuro-sub study on which this paper is based, accommodated for this factor using the method described within the methodology of the research by Phillips et.al.[3]

Previous studies in adult cohorts have shown that adding cognitive screening questions, improves the sensitivity and specificity of the IHDS screening tool. The additional executive function component of this tool, increases its clinical utility further as executive function is known to be particularly affected in YLWH who have HAND.[15]

Conclusion

In conclusion, this study shows that the CAT-rapid v2 - at a cut off score of 17 or less – had reasonable sensitivity. However, the tool does not meet the threshold, generally accepted by clinicians, for sensitivity and specificity in order to reduce the rate of false positives. It is therefore important continue to develop more reliable tools for younger people living with HIV. Clinicians should have a wide range of screening tools available to them. They can then select the most appropriate tool, based on the clinical presentation. We recommend that future research includes a validation study of combined versions of various screening tools, to assess if combining tools improves the sensitivity and specificity in a manner that improves its clinical utility. Additionally, future studies should look into how the different subsections of the tool contribute to the overall sensitivity and specificity of the tool. Ongoing work in the University of Cape Town, HIV mental health research unit will take these matters into consideration within the ongoing research being conducted.

Appendix A

Cognitive Assessment Tool- Rapid Version (CAT-Rapid)[1]

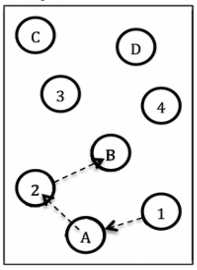
1. Symptoms- *Ask the patient the following questions exactly as they are written*:
"Compared to your best:
- do you often have problems remembering information? Y=0 N=1
- are your hands clumsy, shaky or weak? Y=0 N=1
- have you found it hard to follow a conversation or a story? Y=0 N=1
- do you have trouble planning or doing daily activities? Y=0 N=1 ___/ 4

2

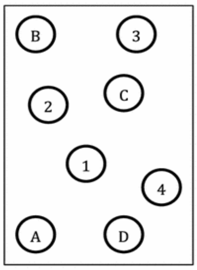
Word Registration- *Give 4 words to recall (apple, watch, table, red), reading one second for each. Ask the patient to repeat them. If not correct say words again. Tell patient you will ask for all 4 words a bit later.*

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. 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: ___/ 4

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 judgement and performing investigations as indicated. Consider referring for further opinion or testing.

International HIV Dementia Scale (IHDS)

1

Memory-Registration – Give four words to recall (dog, hat, bean, red) – 1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

1. Motor Speed: Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.
   4 = 15 in 5 seconds
   3 = 11-14 in 5 seconds
   2 = 7-10 in 5 seconds
   1 = 3-6 in 5 seconds
   0 = 0-2 in 5 seconds
   ____

2. Psychomotor Speed: Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5th digit. Demonstrate and have patient perform twice for practice.
   4 = 4 sequences in 10 seconds
   3 = 3 sequences in 10 seconds
   2 = 2 sequences in 10 seconds
   1 = 1 sequence in 10 seconds
   0 = unable to perform
   ____

3. Memory-Recall: Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).
   Give 1 point for each word spontaneously recalled.
   Give 0.5 points for each correct answer after prompting
   Maximum – 4 points.
   ____

Total International HIV Dementia Scale Score: This is the sum of the scores on items 1-3. The maximum possible score is 12 points. A patient with a score of ≤10 should be evaluated further for possible dementia.

____

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y-IHDS = additional time to practice the motor and verbal memory tasks

= additional question on having ever repeated a grade

3

1 + 2 +3 = 4

HIV Mental Health
Research Unit

CAT-RAPID

Name:

Date:

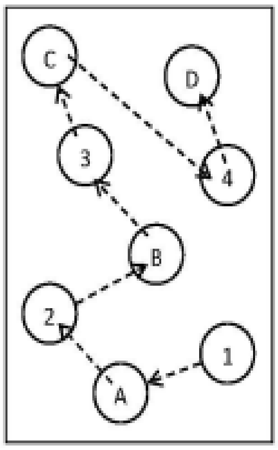
COGNITIVE ASSESSMENT TOOL- RAPID VERSION 2.0

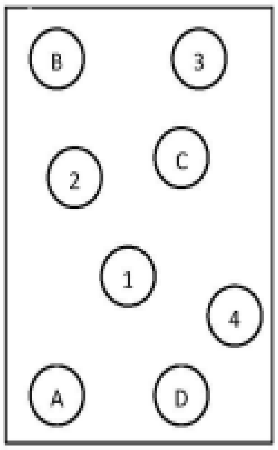
SYMPTOMS

Do you often have problems remember ng 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

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.





1-A =1
A-2-B =1
B-3-C =1
C-4-D =1
/4

fold here

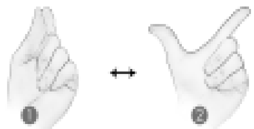
WORD REGISTRATION

Give 4 words to recall, 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.

APPLE WATCH TABLE RED

MOTOR SPEED

Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible. Record how many taps they can perform in 5 seconds.



4= 15 in 5 sec
3= 11-14 in 5 sec
2=7-10 in 5 sec
1=3-6 in 5 sec
0=0-2 in 5 sec /4

PSYCHOMOTOR SPEED

Have the patient perform the pictured movements with the non-dominant hand as quickly as possible. Demonstrate and have the patient perform the sequence twice for practice. Record how many sequences they can perform in 10 seconds.

4= 4 sequences in 10 sec
3= 3 sequences in 10 sec
2=2 sequences in 10 sec
1=1 sequences in 10 sec
0=0 sequences in 10 sec /4

WORD RECALL

Ask the patient to recall the 4 words. For words not recalled, provide a clue.

Apple = 1	**"Fruit" = ½**
Watch = 1	**"Jewelry"= ½**
Table = 1	**"Furniture" = ½**
Red =1	**"Colour" = ½**

/4

TOTAL

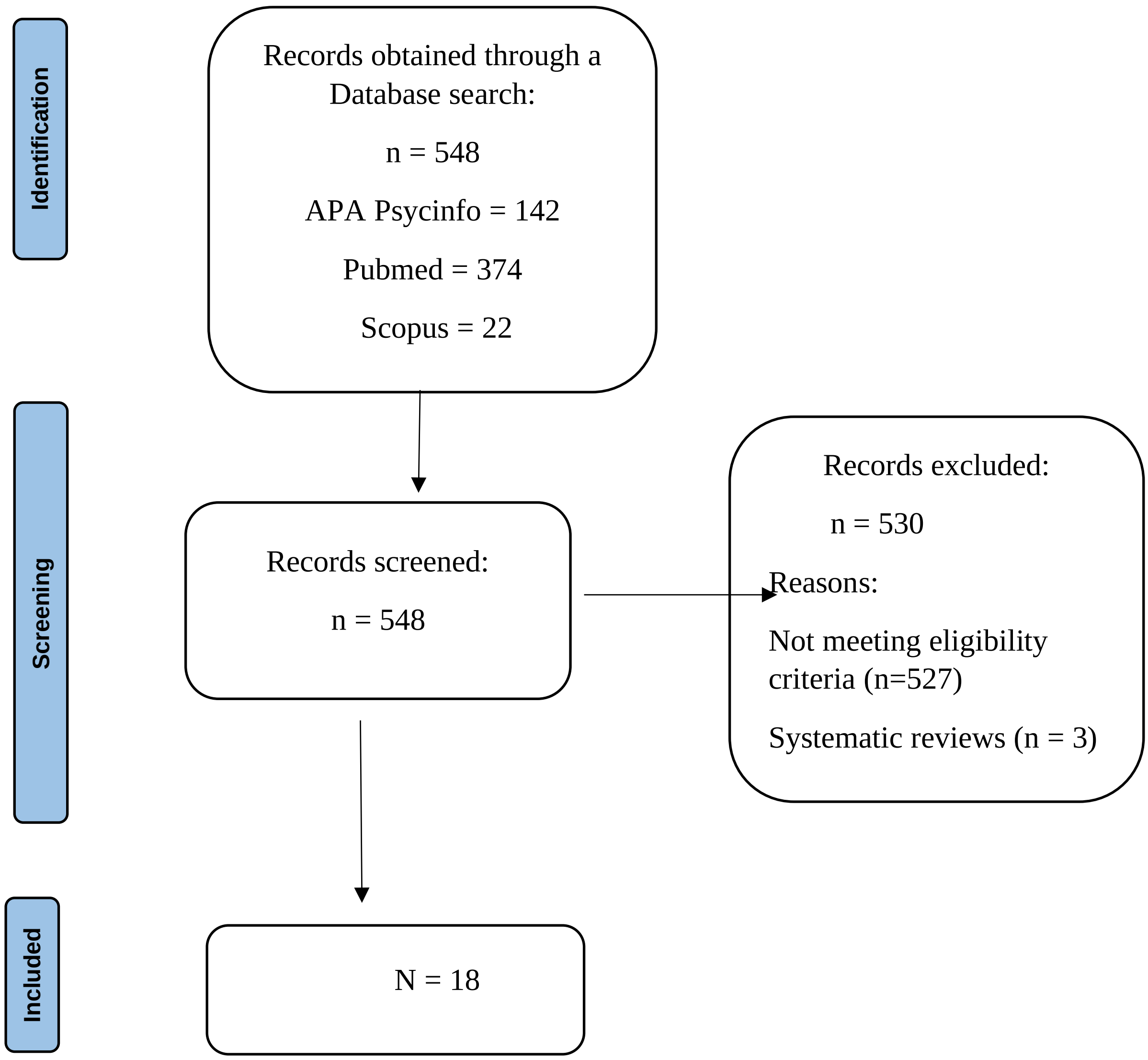
Cut-off score of ≤16 /20

4

Appendix B

Documentation related to the Systematic review

Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram detailing the identification of eligible studies: [1]



Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
1. [2]	Musindo O et al. 2018	Neurocognitive functioning of HIV positive children: exploring neurocognitive deficits and psychosocial risk factors.	To assess the neurocognitive function of HIV infected children and adolescents and correlate it with psychosocial factors.	Kaufman Assessment Battery for Children-Second Edition was used to assess cognitive function and psychosocial issues were assessed using HEADS-ED	Prevalence of neurocognitive deficits was 60%. The extent of the deficits was not associated with low CD4 count, high viral load, or early initiation in HIV care.	Poor school performance and problems with peers was associated with poor neurocognitive performance. The implications being that there must be a stronger emphasis on peer relations and scholastic support in children living with HIV.
2. [3]	Nichols S.L et al 2013	Neurocognitive functioning in antiretroviral therapy–naïve youth	To characterize the prevalence and clinical correlates of HAND in youth living with HIV	Completed a comprehensive neurocognitive, substance use, and behavioral health assessment battery.	67% of youth met criteria for HAND (96.4% were asymptomatic and 3.5% were syndromic); deficits in episodic memory and fine-motor skills emerged as the most commonly affected ability areas.	The study highlights the high prevalence of HAND in this population group, majority of which are asymptomatic. It also highlights the need to actively screen for neurocognitive impairment in YLWH.

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
3. [4]	Philips NJ. et al. 2018	HIV-associated cognitive disorders in perinatally infected children and adolescents: A novel composite cognitive domains score.	They compared the efficacy of global cognitive scores to that of composite cognitive domain scores in detecting cognitive disorders in a sample of perinatally HIV-infected children, and a demographically matched HIV negative control group.	A comprehensive neuropsychological test battery was administered.	Comparison of a global cognitive score to composite domain scores suggested that the latter provided more detailed information when compared to global scores and were more sensitive in detecting HIV-associated cognitive disorders.	The authors suggest that a composite domain score may give a more accurate assessment of cognition which may assist with comparisons across regions and cultures globally.
4. [5]	Hoare J. et al. 2016	Applying the HIV-associated neurocognitive disorder diagnostic criteria to HIV-infected youth.	To apply the HIV-associated neurocognitive disorders (HAND) criteria for diagnosing HAND in HIV-infected adults, in a cohort of HIV-infected youth to thus establish whether this system is able to detect a spectrum of	Comprehensive pediatric neurocognitive battery, an assessment of functional competence, and the American Academy of Neurology system for diagnosing ND in a cross-sectional study	HIV-infected youth performed significantly more poorly on tests of Verbal IQ, Full Scale IQ, processing speed, finger tapping, verbal memory, expressive language, cognitive flexibility, and inhibition.	The HAND criterion designed for adults was able to identify youth with important functional cognitive impairments who do not fit criteria for HIVE and would therefore not

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
			neurocognitive disorders (ND) in HIV-infected youth.			have been identified otherwise.
5. [6]	Phillips N. et al. 2021	Youth perinatal HIV-associated neurocognitive disorders: association with functional impairment	To determine whether cognitive impairment is associated with functional impairment and if it carries higher risk for also having functional impairment.	Parent-rated information regarding youth functional impairment on four different measures was collected. A cognitive battery was administered to determine cognitive impairment.	Repeated grades strongly associated with cognitive impairment and functional impairment. When cognitive impairment was present, youth had a higher risk of experiencing functional impairment as well.	Inclusion of a question relating to the number of grades that a youth has repeated is a useful screening question that can then warrant further assessment and monitoring of that youth.
6. [7]	Brassell SE. and Potterton J. 2019	Prevalence of disability in HIV-infected children attending an urban paediatric HIV clinic in Johannesburg, South Africa	To investigate the prevalence of disabilities among a group of HIV infected children in South Africa and whether they are being referred to and accessing support services.	Parents were interviewed about their child using the Ten Question Screen for Disability questionnaire along with a follow-up questionnaire.	50.5% of the children experienced disabilities, where 58.4% of those had more than one co-existing disability. The prevalence of disability	The findings from this study are concerning. Poor access to services is known to be prevalent amongst cognitively impaired HIV positive adults. Children are even more

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
					in children infected with HIV is high and these children are not being referred to and/or accessing the appropriate support services.	vulnerable as they cannot self-present. They often have to rely on adults or caregivers to get them access to the care they need.
7. [8]	Frigati L J. et al. 2019	Multisystem impairment in South African adolescents with Perinatally acquired HIV on antiretroviral therapy (ART)	They investigated the overlapping burden of neurocognitive, cardiovascular, respiratory and/or renal impairment among PHIV positive (PHIV+) adolescents.	Impairment at enrolment was assessed across neurocognitive functioning; cardiac function (echocardiogram abnormality); respiratory function (abnormal spirometry) and renal function (abnormal glomerular filtration rate).	PHIV+ participants who had failed a year of school and with a viral load >1000 were more likely to have dual or multisystem impairment. In those with neurocognitive impairment, almost 60% had additional systems impaired	Failing a Grade in school appears to be a sensitive marker for cognitive impairment and greater psychosocial and functional impairment amongst HIV positive adolescents.
8. [9]	Murthy VS et al. 2018	A study of neuropsychological profile of human	The aim was to study the neuropsychological and functional profile of	Neuropsychological evaluation, Brief Impairment Scale to assess	Significant differences between the verbal, performance intelligence	This study highlights the significant impact that HIV infection had

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
		immunodeficiency virus-positive children and adolescents on antiretroviral therapy	children and adolescents with human immunodeficiency virus (HIV) infection on antiretroviral therapy (ART)	functional impairment, and a semi-structured questionnaire to obtain other relevant details.	quotients (IQs), global IQ score, and several individual subtests between cases and controls. The HIV group was also found to have a significant functional impairment. HIV infection is associated with significant cognitive and functional impairment.	on the developing brain. Highlighting the importance of identifying at risk children and adolescents and intervening timeously to prevent or slow down disease progression and impairment.
9. [10]	Boivin MJ 2020	African Multi-Site 2-Year Neuropsychological Study of School-Age Children Perinatally Infected, Exposed, and Unexposed to Human Immunodeficiency Virus	To evaluate the neuropsychological outcomes, longitudinally among perinatally infected African children who received early	Neuropsychological testing and the Behavior Rating Inventory of Executive Function (BRIEF).	Despite initiation of ART in early childhood and good viral suppression at the time of enrolment the HIV+ group had poorer neuropsychological performance over time,	Important findings that highlight that early initiation of ART still experience poorer cognitive functioning as they reach adolescence. Other strategies thus

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
			antiretroviral treatment (ART).		with the gap progressively worsening in planning/reasoning. This can be debilitating for self-management in adolescence.	need to be considered in addition to ART.
10. [11]	Kerr SJ. 2019	Increased Risk of Executive Function and Emotional Behavioral Problems Among Virologically Well-Controlled Perinatally HIV-Infected Adolescents in Thailand and Cambodia	To examine the cognitive and behavioral outcomes in a longitudinal cohort of Asian youth.	Executive function was assessed with Children's Color Trails Tests 1 and 2 (CCTT-1 and -2), the design fluency test, and the verbal fluency test. Working memory (Freedom from Distractibility Index) and processing speed index were assessed using WISC-III. Visual memory was assessed by design memory and design	Asian adolescents with PHIV remain at risk of cognitive and mental health problems despite HIV treatment. Selective risks are observed among HEU youth.	Confirms findings from other studies that the risk of cognitive impairment remains even in the context of ongoing ART use.

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
				recognition subtests of the Wide Range Assessment of Memory and Learning (WRAML-2) and behavioral problems using the Child Behavior Checklist (CBCL).		
11. [12]	Harris LL. Et al. 2017	Prospective memory (PM) in youth with perinatally-acquired HIV infection	To determine the presence and extent of PM deficits in youth with PHIV	Naturalistic Event-Based Prospective Memory Test (NEPT) and the Prospective Memory Assessment for Children & Youth (PROMACY).	Findings suggest a subset of youth with PHIV (those with a prior AIDS-defining diagnosis) is vulnerable to PM deficits.	Highlights the long-term impact of untreated HIV and the importance of early initiation of ART.
12. [13]	Haase VG. 2014	Executive function and processing speed in Brazilian HIV-infected children and adolescents	To investigate the neuropsychological performance in a cohort of vertically infected Brazilian children and adolescents who	Executive function: digit span, stroop test, semantic word fluency, visual search task, tower of Hanoi task, list discrimination tests.	HIV-infected children and adolescents exhibited lower performance on neuropsychological tasks than age matched controls. controls. Motor and cognitive processing	The authors conclude that executive function and processing speed are the most discriminative domains, yet in this study these two domains are the

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
			underwent antiretroviral therapy	Processing speed: nine-hole peg test, simple articulatory speed.	speed and executive function appears be the most discriminative domains.	only ones that were assessed. Nonetheless, their findings are in keeping with other literature in this area.
13. [14]	Garcia-Navaro C. et al. 2020	Significant differences between verbal and non-verbal intellectual scales on a perinatally HIV-infected cohort: from pediatrics to young adults	To assess the intellectual profile of their cohort, considering both the infection and socio-environmental related variables	Spanish version of the Kaufman Brief Intelligence Test (K-BIT) and semi-structured interviews.	Higher parental education was associated with better performance across all intelligence scales.	Highlights an important potential intervention, that of improving caregiver education levels.
14. [15]	Nichols LS. et al. 2015	Executive Functioning in Children and Adolescents with Perinatal HIV Infection	To examine the associations of EF with HIV infection, disease severity and other factors among youth with PHIV and perinatally HIV-exposed, uninfected youth (PHEU).	Standardized EF measure (Children's Color Trails Test, CCTT) and youth and/or caregivers completed a questionnaire measuring everyday EF (Behavior Rating Inventory of Executive Function, BRIEF)	Youth with PHIV show executive function problems likely associated with risk factors other than HIV.	The authors highlight the importance of identifying other risk factors. These may include stressful life events, poverty and resulting lower environmental or educational enrichment,

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
						parental illness and functional impairment, and family history of psychiatric disorders
15. [16]	Linn K Et Al. 2015	HIV-Related Cognitive Impairment of Orphans in Myanmar with Vertically Transmitted HIV Taking Antiretroviral Therapy	To determine the effect of perinatally acquired HIV on neurocognition in Myanmar children treated with ART in comparison to demographically matched seronegative children.	A battery of cognitive tests sensitive to HIV-associated impairments in children was administered.	Results showed that HIV-infected children performed poorly across all tests, significant group differences in executive function, visuospatial reasoning, fine motor dexterity, and visual motor integration were found.	These results highlight that HIV causes global cognitive impairment in these children.
16. [17]	Sirois PA. 2016	Associations of Memory and Executive Functioning with Academic and Adaptive Functioning	They examined the associations of 2 key neurocognitive domains, memory, and executive	Participants completed standardized measures of reading and math.	Higher-order cognitive abilities such as memory and EF seem to play a key role in academic and	The authors conclude by stating that these higher order cognitive abilities may serve as

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
		Among Youth with Perinatal HIV Exposure and/or Infection	function (EF), with academic and adaptive skills among youth with PHIV and perinatally HIV-exposed but uninfected (PHEU) youth.		adaptive capacities, regardless of a child's HIV status.	important targets for interventions aimed at improving functional outcomes.
17. [18]	Cohen S. 2015	Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls	To compare the neuropsychological profile of perinatally HIV-infected children in the Netherlands to that of matched healthy controls.	Participants completed a neuropsychological assessment evaluating intelligence, information processing speed, attention, memory, executive function, and visual-motor function.	Cognitive performance of HIV-infected children is poor compared with that of SES-matched healthy controls.	The findings are in keeping with those of similar studies and points to the importance of early identification of these cognitive effects to prevent or slow the progression of the decline.
18. [19]	Smith R. 2012	Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence	To examine the cognitive and adaptive functioning of a group of PHIV+ youth and youth who were perinatally HIV-exposed	Youth and caregivers were seen every six months for medical, clinical, and neuropsychological evaluations.	Mean full scale IQ (FSIQ) scores were significantly lower for the PHIV+ group who had a previous history of	Early identification and interventions are vital in this vulnerable group of youth.

Nr	Author & Year	Short Title	Aims	Method	Author Conclusion	Relevance to current study
			but uninfected (PHEU) who share similar demographic and psychosocial characteristics		an AIDS defining illness. This was mainly due to a previous history of encephalopathy.	

Search terms:

1. youth or adolescents or young people or teen or young adults AND HIV or aids or acquired human immunodeficiency syndrome or human immunodeficiency virus AND cognitive impairment or cognitive dysfunction or cognitively impaired, time frame: 2010 -2021.Database APA Psyc info 04/03/2021 at 9am. Yielded 142 records. Eligible studies 7.

   Excluded – adults, imaging studies, duplicates, other psychiatric conditions.

   Included – youth (18 years and younger), cognitive impairment, HIV positive.

2.((youth or adolescents or young people or teen or young adults) AND (hiv or aids or acquired human immunodeficiency syndrome or human immunodeficiency virus)) AND (cognitive impairment or cognitive dysfunction or cognitively impaired). Time frame 2010-2021. Database Pubmeb accessed on 15/03/2021 at 9am.Yielded 374 records. Eligible studies 13.

Excluded – adults, imaging studies, duplicates, other psychiatric conditions.

Included – youth (18 years and younger), cognitive impairment, HIV positive.

3.((youth or adolescents or young people or teen or young adults) AND (hiv or aids or acquired human immunodeficiency syndrome or human immunodeficiency virus)) AND (cognitive impairment or cognitive dysfunction or cognitively impaired). Time frame 2010-2021.Database Scopus, accessed on 06/04/2021.Yielded 22 records. Zero eligible studies found.

Excluded – adults, imaging studies, duplicates, other psychiatric conditions.

Included – youth (18 years and younger), cognitive impairment, HIV positive.

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Appendix C -Summary of Instructions for Authors -AIDS Journal

All manuscript submissions to the regular issues and supplements of the Journal are peer-reviewed. Submitted articles have a preliminary evaluation by the editors, and those considered for publication undergo further assessment by the editors and selected reviewers. The Journal uses a single-blind process for peer-review. Papers may be subject to a statistical analysis. Short comments can be considered as Correspondence: case reports are not encouraged.

Authors should submit their manuscripts through the web-based tracking system at http://aids.edmgr.com/. Authors should NOT in addition then post a hard copy submission to the editorial office. Double spacing should be used throughout the manuscript, which should include the following sections, each starting on a separate sheet: Title Page, abstract (when required) and keywords, text, acknowledgements, references, individual tables and captions. Margins should be at least 3 cm. Pages should be numbered consecutively, beginning with the Title Page, and the page number should be placed in the top right-hand corner of each page. Abbreviations should be defined on their first appearance in the text; those not accepted by international bodies should be avoided. The word count should be clearly stated on the Title Page.

Title Page

The Title Page should carry the full title of the paper (not more than 120 characters) and a short title (not more than 40 characters) to be used as a 'running head' (and which should be so identified). Titles should not contain names of specific studies, a description of the procedures used, or the location of the study. The given or first name, middle initial and family name (surname) of each author should appear. The family name (surname) must appear in CAPITAL letters. If the work is to be attributed to a department or institution, its full name should be included. Total number of words used should be clearly stated on the Title Page. Any disclaimers should appear on the Title Page, as should the name and address (and email) of the author responsible for correspondence concerning the manuscript. Finally, the Title Page should include the sources of any support for the work in the form of grants, equipment, drugs, or any combination of these.

Appendix D - Ethics approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 March 2022

HREC REF: 137/2022

Dr N Phillips
Department of Psychiatry & Mental Health
Neuroscience Institute-GSH
Email: Nicole.phillips@uct.ac.za
Student: Lihle.mgweba@gmail.com

Dear Dr Phillips

PROJECT TITLE: SCREENING FOR HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS IN PERINATALLY INFECTED YOUTH: VALIDATION OF THE CAT RAPID VERSION 2 SCREENING TOOL-MASTERS CANDIDATE-DR LIHLE MGWEBA-BEWANA

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, our letter dated 02 February 2022 provides guidance found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Approval is granted for one year until the 30 March 2023.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Lihle Mgweba-Bewana will also be involved in this study.

Please quote the HREC REF 137/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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